AWARENESS

Newer Horizons in Human Excellence

VOL 2 | ISSUE 1 | JANUARY 2025 https://awarenessjournals.com

About the Journal

The journal Awareness is dedicated to promoting and disseminating knowledge derived from innovative research that serves humanity, all forms of life, and their environments. It aims to foster deeper understanding by integrating empirical, experimental, experiential, and spiritual dimensions of knowledge across diverse disciplines. At its core, the journal seeks to expand the horizons of collaborative and empirical research, motivated by a love for humanity, child-like curiosity, and an unwavering commitment to truth. Awareness aims to be a publicly accessible platform for fresh, creative knowledge and shared scholarly exchange, thus embracing the principle that knowledge, like light, must be shared freely and openly to dispel ignorance and inspire the pursuit of human excellence. Only through such open exchange can the journal fulfill its commitment to the ideals of the University for Human Excellence.

The journal also provides a forum for exploring critical issues related to the advancement of human excellence, welcoming a wide range of perspectives across multiple fields. It publishes original research articles, reviews, perspectives, editorials, commentaries, and book reviews, all of which reflect the personal views of the authors. These contributions do not represent the official stance of the University or the institutions affiliated with the authors, editors, or reviewers, preserving the journal's commitment to intellectual independence and diversity of thought.

JOURNAL PARICULARS

Title	AWARENESS – Newer Horizons in Human Excellence
Frequency	Bi – Annual
ISSN	XXXX-XXXX
Publisher	Sri Sathya Sai University for Human Excellence
Chief Editor	Prof. Kanwaljeet J. S. Anand
Starting Year	2024
Subject	Multidisciplinary
Language	English
Publication format	Online
E-mail ID	awareness.journals@sssuhe.ac.in
Website	https://awarenessjournals.com/
Author Guidelines	https://awarenessjournals.com/author-instructions
Privacy Policy	https://www.awarenessjournals.com/public/img/pdf/privacy-policy.pdf
Copyrights	https://www.awarenessjournals.com/public/img/pdf/copyrights-permissions-policy.pdf

SRI SATHYA SAI UNIVERSITY FOR HUMAN EXCELLENCE
योगः कर्मसु कौशलम्

SRI SATHYA SAI
UNIVERSITY FOR
HUMAN EXCELLENCE

AWARENESS

Newer Horizons in Human Excellence

Table of Contents

SRI SATHYA SAI UNIVERSITY FOR HUMAN EXCELLENCE
योगः कर्मसु कौशलम्

Editorial

Growing *Awareness*

Kanwaljeet J. S. Anand, MBBS, D.Phil.; Shaun P. Setty, M.D.

Stanford University of Medicine, Stanford, California, USA.

Correspondence: anandam@stanford.edu Tel:+1-650-498-6313

Keywords: knowledge, evidence, wisdom, understanding, growth

Homo sapiens, based on current evidence, evolved from its hominid predecessors about 320,000 years ago[1] and thence started mankind's search for new knowledge. The innate desire to seek, to learn, to experience, and to understand, have existed since time immemorial. Human understanding, however, made a great leap forward about 70,000 years ago when the early humans developed the ability to communicate and share knowledge through language, to build social bonds through storytelling, and to discuss abstract concepts such as love, beauty, and spirituality. These newfound abilities enabled us to learn from each other through teaching, imitation, and other forms of transmitting knowledge. Each recurring connection and event allowed the species to evolve over time.

Another surge in human understanding and awareness occurred about 12,000 years ago in the Neolithic Age with the first Agricultural Revolution, when humans transitioned from a hunter-gatherer lifestyle to one of farming and settlement. As migrant human groups evolved into hierarchical societies, they could transmit their common knowledge from generation to generation through culture, common practices, and rituals that were unique to each group. This process changed how we as humans lived, ate, interacted, and reproduced, as knowledge of farming and animal husbandry was passed from generation to generation through cultural transmission, paving the way for our modern civilization[2].

The earliest efforts to record human knowledge led to cuneiform writing, by making marks in wet clay with a reed straw. Other uses of the common reed included its use as thatching or construction material, making baskets, rafts, boats, musical instruments, and even arrows for hunting. Early writings increased our ability to transmit knowledge from generation to generation, and even within the same generation, thus permitting the growth and structure of large, complex societies[3]. Human societies enabled academic learning and training of the young, with the free exchange of information leading to a growth in human awareness - thus fueling the agricultural, industrial, and technological revolutions. The recent Digital Revolution, it appears, may be having the opposite effects with declining human awareness - as we humans become more connected with our devices rather than with our natural and social environments[4,5].

"Awareness" is a unique human perception without which nothing else has any meaning, any value. The awareness of an ant or, for that matter, any other life form is limited to its natural environment and its functions. As the species evolve, the range and contents of their awareness also continue to

Citation: Anand K.J.S., Setty S.P.; *Awareness*, 2 (1): 1-3

Academic Editor: None

Received: Dec. 28, 2024

Revised: Dec. 30, 2024

Published: Jan. 14, 2025

grow and expand. Eventually, as humans we become aware of our 'animus', our sense of an animating presence, a perception of ourselves as conscious beings, without which we cannot know anything or enjoy anything. It is, literally, the core of our being! This most precious 'presence' manifests as consciousness in all embodied forms, which energizes all their senses, their sense perceptions, and their activities…. and each organism wants to protect it at any cost. Only when consciousness seeks its own source (only possible as humans) and recognizes that it is nothing except consciousness - a clear apperception of that truth becomes permanent and irrevocable. As this realization dawns, all the differences between 'self' and 'others' disappear, giving rise to an intense, unlimited, unconditional love for all. Such a reali-zation cannot diluted, or destroyed, or distracted by any 'thing' within the manifest universe - whether that's a place, person, or situation. This perception exists beyond Time and Space, and it has been labeled variously as 'liberation' or 'enlightenment' or some other terminology among all the world's religions and faith traditions. Gaining this apperception is verily the final goal of human consciousness, and of Creation itself!

Growing ***Awareness*** as a journal in the past year has followed pretty much the same trajectory as that of the spiritual seeker, a search in which the seeker becomes the sought. Just as the initial stages of any spiritual journey are fraught with innumerable hurdles and difficulties, this journal had to deal with its own share of snags and struggles. Following the muted success of its inaugural issue[6], the main goals for ***Awareness*** were to: (a) grow its multidisciplinary Editorial Board, (b) launch an accessible and functional website, (c) create an online presence in scholarly or academic circles, as well as through social media, (d) apply for and obtain an ISSN number, and (e) encourage an increasing number of manuscript submissions.

Variable degrees of success were achieved on all of these fronts. Membership of the Editorial Board has doubled in the past year. A logo was created for the journal and a domain name purchased for the journal website, which is currently at its 3rd generation with the updates and modifications to enhance its functionality. An online presence in academic circles and on social media still remains an aspirational goal at present, given the journal's limited resources and the limited bandwidth and talents of its editorial team. Our search continues for dedicated volunteers who can serve as our webmaster and social media coordinator to take over these areas of responsibility.

This far we've come, and yet the journey has just begun. We resolve that the coming year will quadruple the number of manuscript submissions, with greater variety and range - particularly for the arts & humanities, as well as business & commerce sections. We also plan to start a Student's Corner in this journal, so that the upcoming generations are given the space to express themselves and they are also coached by our erudite Editorial Board Members into the intricate art of effective writing. From expanding the scope of this journal, to further building the breadth and depth of expertise available on its Editorial Board, to appointing Section Editors for each section, to countering the unique challenges of Artificial Intelligence (AI), fake scholarly submissions, and plagiarism - we are certain that growing Awareness will always remain a most enjoyable and fruitful journey. When one fathoms the extent of how far the human species has come and the exponential growth it has proven over the last millennium, it serves that we also examine our own inner self and bring ourselves back to the core roots of what makes us human. It is this goal that the journal proves to explore, one that shows that the many disciplines are more alike than they are different and one that proves to make us "aware" of the meaning of Life Itself.

Supplementary Materials: None.

Author Contributions: Dr. Anand created the first draft of this Editorial; Dr. Setty revised it and added critical content; both authors are in agreement with the final version.

Funding: None.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: None.

Conflicts of Interest: None.

References

1. Delson E. An early dispersal of modern humans from Africa to Greece. Nature. Jul 2019;571(7766):487-488. doi:10.1038/d41586-019-02075-9
2. Crema ER, Kandler A, Shennan S. Revealing patterns of cultural transmission from frequency data: equilibrium and non-equilibrium assumptions. Sci Rep. Dec 15 2016;6:39122. doi:10.1038/srep39122
3. Kaniewski D, Van Campo E, Van Lerberghe K, et al. The Sea Peoples, from cuneiform tablets to carbon dating. PLoS One. 2011;6(6):e20232. doi:10.1371/journal.pone.0020232
4. Hoehe MR, Thibaut F. Going digital: how technology use may influence human brains and behavior . Dialogues Clin Neurosci. Jun 2020;22(2):93-97. doi:10.31887/DCNS.2020.22.2/mhoehe
5. Shanmugasundaram M, Tamilarasu A. The impact of digital technology, social media, and artificial intelligence on cognitive functions: a review. Frontiers in Cognition. 2023;2:1203077. doi:https://doi.org/10.3389/fcogn.2023.1203077
6. Anand KJS, Setty SP. Striving for perfection. Awareness. 2024;1(1):27-29.

Perspective

Molecular basis of fingerprint pattern formation

Nallur B. Ramachandra, Ph.D.

DAE-Raja Ramanna Chair, Department of Studies in Genetics and Genomics, University of Mysore

Correspondence: nallurbr@gmail.com Tel:+91 98800-33687

Abstract: The fingerprints are an individual's genetically determined unique epidermal ridge patterns that remain constant throughout life. For centuries, man has used fingerprints for fortune-telling and as proof of a person's identity. Glover et al., [1] recently published an interesting article that aims to understand the developmental basis of fingerprint pattern formation and variation. The fingerprint ridges undergo a trun-cated hair follicle developmental program with differential gene expression and signaling of molecular players. Cell proliferation in several spreading waves initiated at variable sites delivers uniqueness to each fingerprint. Here, I present an overview of the historical background, a concise review of the molecular mechanisms and the implications of fingerprinting technology.

Keywords: fingerprints, genes, epidermal ridges, signaling, patterning

Citation: Ramachandra N. B.; . *Awareness*, 2 (1): 4-7

Academic Editor: Dr. B. K. Thelma

Received: Aug. 24, 2024

Revised: Dec. 04, 2024

Accepted: Dec. 19, 2024

Published: Jan. 14, 2025

1. Introduction

Fingerprinting captures the unique impression of ridges on an individual's palms, digits, and soles. The ridges on the skin surface enhance grip and discriminate texture. The most common types of fingerprint ridge patterns are loops (65 %), whorls (30 %) and arches (5 %) (Figure 1). Loops are ridges that curve only on one extremity of the pattern. The ridges that encircle a core are the whorls in an anticlockwise or clockwise. The arch is the simple ridge passing from one digit margin to another. Fingerprints are not the same in both hands and persist lifelong unless the dermis is damaged. The likelihood of seeing identical fingerprints was 1 in 64 million. The fingerprint is unique for an individual be-cause the epidermal ridges are genetically determined, and their patterns remain con-stant throughout life. Nongenetic factors may also influence the inheritance of fingerprint patterns [2-3].

For centuries, man has used fingerprints for fortune-telling and as proof of an individual's identity. The history of skin ridges and their applications was reviewed by Galton [4]. In 1929, Harold Cummins and Charles Midlo published the remarkable book "Fingerprints, Palms and Soles" [5]. In 1976, Schaumann and Alter published a book titled "Dermatoglyphics in Medical Disorders". Li et al., [6] reported that limb development genes underlie variation in a human fingerprint pattern. Glover et al., [1] recently published exciting articles on the developmental basis of fingerprint pattern formation and variation. Here, I summarize the key findings of Glover et al., [1] highlighting the molecular mechanisms involved in the fingerprint pattern.

2. Molecular mechanisms in fingerprint patterning

Glover et al., [1] demonstrated the developmental basis of fingerprint pattern formation and variation using fetal specimens, cell lines and mice as experimental materials, employed several staining methods, in situ hybridization, single nucleus RNA sequencing, ridge and hair placode markers, skin organoids, fibroblast and ex vivo skin cultures, qPCR, atomic force microscope for cell density, primary ridge morphology and proliferation analysis, mouse digit ridge and flexion crease analysis as well as mathematical simulations. The following paragraphs provide an overview of notable findings on fingerprint patterning.

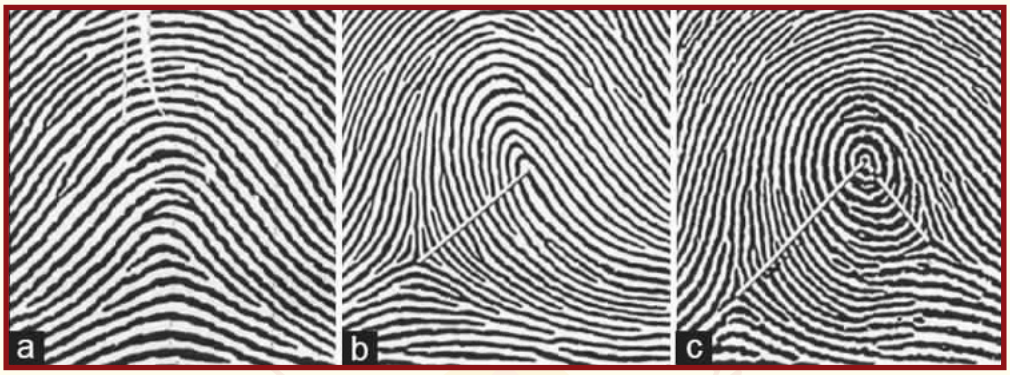


Figure 1. Common types of ridge pattern. a) Arch, b) Loop, and c) Whorl [7].

The early fingerprint ridges are epithelial buds molecularly analogous to hair placodes. The human body carries hair follicles (HF), which express EDAR and WNT pathway genes during embryonic development as circular epithelial placodes. Each placode recruits a dermal condensate by emitting an FGF20 signal and undergoes extended tubular down growth driven by SHH signaling. The volar (hairless) skin from week 8 carries a series of flexion creases across the palm and digit. The expression of EDAR, FGF20, and BMP2 proteins is identical across all the creases, indicating that crease epithelium remains competent to undergo patterning with normal epidermal polarity and organization [8].

The volar epithelium is the first on the body to differentiate into a keratinized, stratified epidermis with lower WNT activity to form a dermal condensate and for aggregation responses to FGF20 signals. In the deepest part of the ridges, FGF20 promotes mesenchymal cell adhesion with the highest WNT/b-catenin activity and retains EDAR and LEF1 expression throughout their proliferative down growth. The primary digit ridges express the early markers as that of HF like EDAR, FGF20 and BMP2, but not the specific HF markers SHH6, SOX2 and DKK1, indicating that primary ridges undergo truncated hair placode development. Single-cell expression profiling identifies LMX1A, TGFA, MYB, and MEGF11, the selective markers as-sociated with ridge and sweat glands, but not HF. High levels of BMP signaling and expression of ENGRAILED in the ridges contribute to the suppression of HF formation in volar skin.

The fingerprints initiate in weeks 12th to 13th when cells in the middle basal layer of the skin start growing faster than the inner or outer layers of the skin. These extra cells are responsible for forming the skin to fold into ridges at the tips of the digits. EDAR expression in the ventral digit epithelium is uniform at week 12 and localized, with high expression at weeks 13 and 14 to the nascent ridges into bands and diminishing in inner ridges. This makes the boundaries at the nail bed and dorsal-ventral boundary of digit skin. By week 15, the primary ridges form the arch, loop, or whorl pattern by interaction with anatomical landmarks. By week 17, the primary ridges carry periodic down growths of sweat glands with higher expression of TGFA and become flanked by smaller secondary ridges, resulting in parallel ridges and grooves of the skin surface.

In volar skin, higher BMP activity was detected throughout the ridge and interridge basal epithelium. The expression of EDAR and WNT signaling is responsible for partitioning the epithelium into ridges and interridges by banded proliferation. Elegant experiments involving inhibition of WNT and ablation of EDAR signaling

confirmed that EDAR is required for normal ridge patterning, and its effects on the size, spacing, and shape of the digit ridges indicate the operation of a spatial patterns and diffusion system in defining their arrangement. The high WNT signaling promotes and drives cellular proliferation and the emergence of morphological ridges and binding to BMPs in interridges to prevent BMPs from binding to their receptors on the cell surface. This indicates that BMP is responsible primarily for patterning signals, and WNT signaling activates cell cycle progression in progenitor and stem cells, defining the spacing interval between ridges. Thus, the interacting WNT and BMP signalling defines the spacing interval between ridges. It is evident that development is complete by the 21st week. One can reproduce the major pattern types of arch, loop, and whorl by manipulating the in-itiation sites' relative timing, location, and angle. The operation of a simple patterning system that reads distal limb geometry to trigger initiation events and the subsequent collision of spreading patterning waves is capable of generating many different types of human fingerprint patterns.

In conclusion, fingerprinting ridges are developmentally abbreviated ectodermal appendages. The early fingerprint ridges are epithelial buds molecularly analogous to hair placodes. The fingerprint ridges do not recruit mesenchymal cells or express late HF markers. Several common and specific molecular signaling are responsible for the development patterning of fingerprints. The interacting WNT and BMP signaling defines the spacing interval between ridges. Further, the ridge initiations from anatomically variable sites determine fingerprint pattern type.

Even though a substantial amount of experimental data has been generated, a more comprehensive presentation of the findings would have enhanced the clarity of gene activity cascades and signaling.

3. Limitations of the study

Although extensive experiments have been carried out, there are many limitations to the current study. Ridge inhibitory factors other than BMPs have yet to be explored and may act in the patterning process. Secondly, the small size of the mouse digit prevents the elaboration of complex ridge patterns in understanding mechanisms defining ridge-to-ridge periodicity. Thirdly, in vivo experiments in humans to understand fingerprint patterning are not possible. To address this issue, longer-term culture methods or organoids that specifically model volar skin formation must be developed. These limitations should be addressed in future studies.

4. Implications of fingerprinting technology

Currently, biometrics is being used widely across the globe for accurately identifying and authenticating an individual. It has various applications ranging from personal devices to corporate security systems, making everyday transactions safer and adaptable to diverse environments. The types of biometrics are fingerprints, ears, iris, and retinal identification, DNA matching, hand geometry, voice, facial, signature and body recog-nition. The patterns of ridges found on the fingertips of humans are the most prominent and widely accepted biometric traits due to their uniqueness, permanence, storability, high indispensability, universality, collectability and performance. Medical uses of fingerprinting aim to solve patient matching, identification and diagnosis of genetic abnormalities. Fingerprinting is also used to identify criminals, trace the drugs ingested, improve security and many more. With the advent of technology, the automated fingerprint identification computer system was developed and implemented on a large scale to improve and expedite the process of maintaining, searching and matching fingerprints in computerized databases. Fingerprint verification technology has become critical in our daily lives as an access key for everything from smartphones and computers to bank accounts, offices, and even health records. Most of the world's population owns Smartphones with built-in biometrics capabilities. In many fields, such as airlines, airports, hotels, telehealth, mobile payments, online retail, e-commerce, and hospitality, companies are integrating mobile biometric authentication into their identity verification processes to enable seamless, secure services and amenities.

Although Smartphone biometrics provides robust security, they are only partially foolproof. Biometric data can be manipulated using high-resolution photos or sophisticated 3D-printed replicas. To address the challenges in mobile biometric authentication, robust encryption, continuous improvement in accuracy, and user education are crucial. Manufacturers are continuously improving their algorithms to combat such attacks.

Author Contribution: The entire article was conceptualized and written by Dr. Rama-chandra.

Supplementary Materials: No supplementary materials.

Funding: No funding was received for this article.

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable

Data Availability Statement: Not applicable

Acknowledgement: I thank DAE for the Raja Ramanna Chair grant, and the University of Mysore for providing me the place of work.

Conflicts of Interest: None.

References

1. Glover JD et al., The developmental basis of fingerprint pattern formation and variation, Cell, 2023,.186: 940–956, www.doi.org/10.1016/j.cell.2023.01.015.
2. Barnes JG, Fingerprint sourcebook – Chapter 1: History, NCJRS Virtual Library, Office of Justice Programs, USA, 2010.
3. Saxena N et al., An updated classification of hair follicle morphogenesis. Exp. Dermatol. 2019, 28, 332–344. www.doi.org/10.1111/exd.13913
4. Galton F, Personal identification and description, Nature, 1888, 38:173-177. https://www.nature.com/articles/038173b0.
5. Cummins H, and Midlo C, Fingerprints, Palms and Soles: An Introduction to Dermatoglyphics. New York: Dover Publication Inc., 1961.
6. Li et al., Limb development genes underlie variation in human fingerprint patterns. Cell, 2022, 6; 185(1): 95–112.e18. www.doi.org/10.1016/j.cell.2021.12.008.
7. https://www.google.com/search?q=fingerprint+images+free+download accessed on 21.08.2024
8. Glover, JD , et al., Hierarchical patterning modes orchestrate hair follicle morphogenesis. PLoS Biol. 2017:15, e2002117. www.doi.org/10.1371/journal.pbio.2002117.

Narrative Review

Single-Cell Analysis for Alzheimer's: Integrating Transcriptomics and Synthetic Biology

Nagashri Nanjundeshwara, Archana Lakshmaiah, Ramya Raghavan

Department of Life Science, Sri Sathya Sai University for Human Excellence, Kalaburagi, Karnataka, 585313, India.

ORCID ID of corresponding author: https://orcid.org/0000-0002-9953-543X

Correspondence: ramya.r@sssuhe.ac.in

Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disorder characterised by progressive cognitive decline. Single-cell transcriptomics has unveiled the complex cellular landscape of Alzheimer's disease (AD), revealing distinct disease-associated cell states and gene expression profiles. This information provides a crucial foundation for leveraging the power of synthetic biology to develop targeted interventions. This paper explores the integration of these two fields, focusing on applications such as: 1) using transcriptomic data to design cell-type-specific synthetic constructs; 2) modelling and manipulating disease-relevant cell-cell interactions; and 3) engineering therapeutic cells for targeted drug delivery or immunomodulation. We discuss the potential of this integrated approach to advance our understanding of AD pathogenesis and pave the way for innovative therapeutic strategies, while also considering the associated challenges and future directions.

Keywords: Synthetic Biology, Bioengineering, Spatial Transcriptomics, Synthetic Gene Circuit, Multi-Omics, Neural Circuit

Citation: Nanjundeshwara N., et al.; *Awareness*, 2 (1): 8-20.

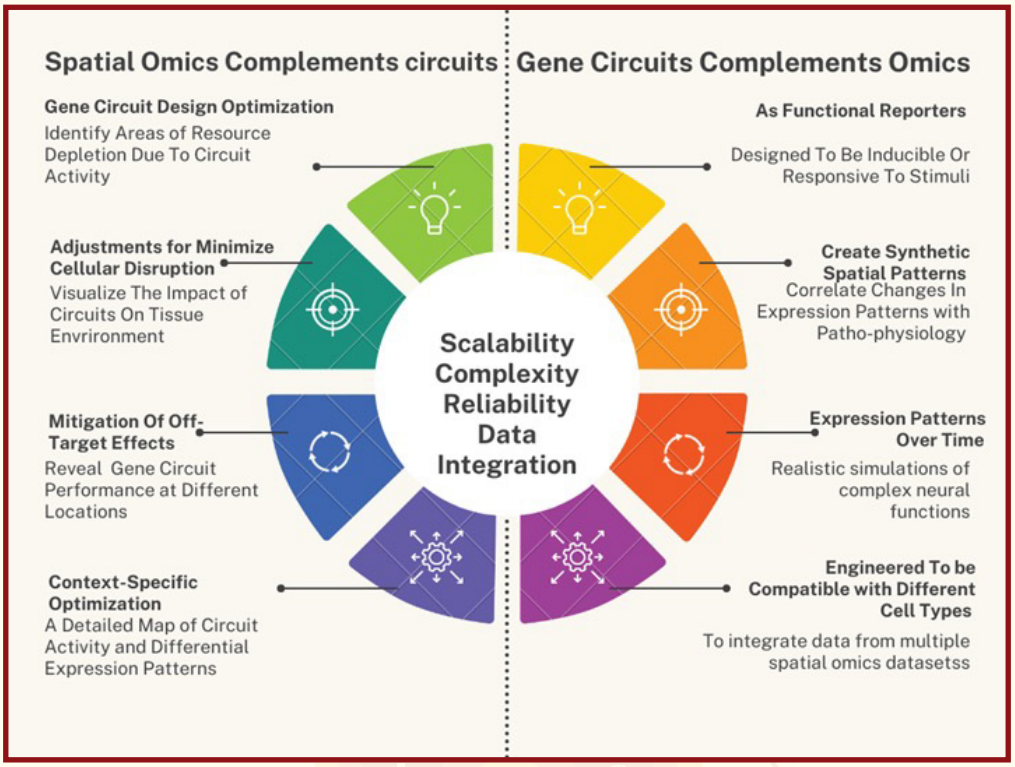
Academic Editor: Dr. N. B. Ramachandra

Received: Jun. 11, 2024

Revised: Dec. 13, 2024

Accepted: Dec. 19, 2024

Published: Jan. 14. 2025



Graphical Abstract: Spatial Omics and Gene Circuits complement each other to overcome challenges and limitations.

1. Introduction

Impaired neurogenesis contributes to neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and Lewy Body dementia in several ways. Amyloid β protein (Aβ) in neuritic plaques of Alzheimer's disease (AD) has been considered the molecular driver of Alzheimer's pathogenesis and progression [1]. Spatial omics technologies, such as spatial transcriptomics (ST) and spatial isoform transcriptomics, provide a means of studying gene expression in tissue architecture and spatial organisation [2]. For example, ST studies have identified disease-associated microglia, which exhibit unique gene expression profiles and functional properties compared to homeostatic microglia. Similarly, distinct subtypes of astrocytes and neurons with altered gene expression patterns have been identified in AD brains.

Single-cell multi-omics technologies enable direct measurement of cell-specific responses, perturbations, and signalling pathways in disease pathogenesis. This provides insights into cellular spatial location, gene expression variations, genetic risk factors like APOE4, and single-cell or subcellular patterns with high spatial resolution. [3]. Spatial isoform transcriptomics (SiT) enables explicitly the characterisation of isoform expression and sequence heterogeneity at a spatial resolution using long-read sequencing. Spatial isoform transcriptomics involves characterising regional isoform switching and differential isoform usage for genes related to specific functions like brain activity [4]. Recent studies have identified rare subsets of immune cells infiltrating the brain in AD, which may contribute to neuroinflammation.

Advances in spatial transcriptomics, such as the 10x Genomics Visium platform, have provided detailed molecular maps that surpass the limitations of single-cell RNA sequencing methods [5]. ST platforms has enabled sub-regional gene expression analysis and comparable sequencing depth for gene number per spot [6]. Developments in super-resolution and expansion microscopy offer higher spatial resolution in omics, enabling visualization of cellular details and interactions crucial for understanding neural circuits.

Table 1. Examples of Spatial Omics Techniques in Alzheimer's Research

Technique	Alzheimer's Research Applications
Multiplex Fluorescent in Situ Hybridization (FISH)	Quantifies expression levels of Alzheimer's-related genes, such as APP, tau, and APOE, in different cell types [22]
RNA Sequencing (RNA-seq) Combined with Imaging	Identifies differentially expressed genes in Alzheimer's disease brain regions, such as the hippocampus and cortex[23] [24].
Imaging Mass Cytometry	Quantifies the expression of Alzheimer's-related proteins, such as amyloid-beta and tau, in different cell types. [22]
Single-cell RNA Sequencing (scRNA-seq) Combined with Imaging	Identifies distinct cell populations involved in AD. Identifies genetic risk factors such as APP, tau, and APOE gene[25] [5]
Super-Resolution Imaging	Super-Resolution Imaging At high resolution, examine the distribution and interactions of Alzheimer's-related proteins, such as amyloid-beta plaques and tau tangles. [26] [27]

2. Synthetic Biology for AD Research:

Synthetic biology engineer cells or organisms to recapitulate AD hallmarks like Aβ aggregation, tau hyperphosphorylation, and neuroinflammation. Gene circuit technology controls gene expression in response to signals, enabling the design of circuits that mimic or modulate AD pathways. Here are some synthetic biology applications:

2.1 Designer Receptors Exclusively Activated by Designer Drugs (DREADDs)

DREADDs are engineered G protein-coupled receptors (GPCRs) that are selectively activated by synthetic ligands (like CNO and clozapine-N-oxide). Chemogenetic manipulation of astrocyte activity using DREADDs can improve neuronal function and behaviour in normal animals and disease models. Different DREADD variants (e.g., hM3Dq for activation, hM4Di for inhibition) can activate or inhibit specific neuronal populations in specific cell types. They allow researchers to control neuronal activity with high temporal and cell-type specificity remotely [8] [9].

2.2 BRANEnet

BRANEnet (Brain Research through Advancing Neurotechnologies) is leveraging advanced molecular genetics techniques. The Alzheimer's disease risk gene BIN1 is critical in regulating calcium homeostasis, electrical activity, and gene expression in glutamatergic neurons. BRANEnet utilises single-cell RNA sequencing, epigenomic analyses, and genome-wide association studies to provide deeper insights into AD [10]. Studies have shown that BIN1 knockout human-induced neurons (hiNs) exhibit reduced activity-dependent internalisation and higher expression of the L-type voltage-gated calcium channel Cav1.2, which affects neuronal calcium transients and electrical activity[11]. The insights gained from circuit omics can inform the design of gene therapies targeted to specific neural circuits, such as the entorhinal cortex-hippocampal (EC-HPC) system in AD patients [12]. BRANEnet aids in understanding microglia, immune cells, and the impact of

genetic risk factors like APOE mutations. By integrating multi-omics data, BRANEnet outperforms baseline methods in tasks like transcription factor target prediction and network inference. Using a random walk-based Positive Pointwise Mutual Information matrix, BRANEnet captures relevant context for understanding complex neural interactions [13].

2.3 Viral Delivery Systems

Contemporary viral tracing strategies and activity recording methods investigate circuit architecture and function. The rapid advancement of CRISPR and anti-CRISPR tools enhances the robustness and applicability of synthetic biology systems. This system includes a genetic circuit that consists of libraries of guide RNAs, synthetic operators, transcriptional activators, and other regulatory elements [14]. Synthetic gene circuits enable permanent neural ensemble labelling, crucial for understanding memory dynamics. Designer cells, autonomous closed-loop therapeutic cells, avoid repeated inducer administration. Genetic devices like toggle switches and repressilators regulate cellular processes. Designer cells with sensing modules detect disease markers and trigger therapeutic agent secretion without external inducers [15] [16].

Optogenetics combines optics and genetics to control specific neurons using photosensitive proteins encoded by adenoviruses. This technique allows for precise ion flow control across cell membranes, leading to inhibition or activation effects [17]. Intersectional genetic approaches and activity-dependent recombinases target specific neuronal populations based on molecular markers or activity patterns, allowing for more refined manipulation of neural circuits [18]. Advances in spatial omics and neuroscience, including optogenetics and synthetic biology, continue to deepen our understanding and ability to manipulate these vital cells for therapeutic purposes [19] [20]. Pseudotyped rabies virus maps monosynaptic connections with cell-type specificity. Genetically encoded indicators reveal neural circuit function in awake animals. Trans-neuronal tracing techniques like HSV-1 H129 and rabies virus map cell-type-specific AD circuits. Multiplexed mapping and sequencing (MAPseq, BRICseq) refine connectivity analysis with single-cell resolution. [15].

2.4 E-SARE and RAM Synthetic Promoters

The RAM promoter enhances IEG labelling for better neuronal activity tracking. Synthetic promoters like E-SARE boost neuronal activation in vivo, aiding neural circuit studies. These promoters can create biosensors and complex circuits with novel functions, advancing our understanding of memory and behaviour [21].

3. Rationale for Integrating Transcriptomics and Synthetic Biology:

Transcriptomic data can inform the design of synthetic constructs that target specific cell types or pathways implicated in AD, leading to more precise and effective interventions. Additionally, an integrated systems-level understanding of AD-associated neural circuit mechanisms requires new multimodal and multi-scale interrogations to study and treat circuits vulnerable to AD. Transcriptomics can reveal how different cell types communicate in the AD brain. At the same time, synthetic biology can be used to engineer model systems to study these interactions in a controlled manner [28] [29].

3.1 Synthetic receptor systems

Synthetic receptors are potent tools in cell and gene therapies, allowing for precise control of therapeutic cells and genetic modules. These receptors can regulate the production of bioactive payloads by sensing and processing user-defined signals or biomarkers. Examples of synthetic receptor systems include chimeric antigen receptors (CARs) and synthetic Notch (synNotch) receptors [30] [31].

3.2 Advantages over traditional methods:

- Specificity: Synthetic receptors offer high specificity for their ligands, minimising off-target effects.
- Temporal control: The timing of receptor activation can be precisely controlled.
- Modularity: Synthetic receptors can be easily modified or combined to create new functionalities.

Synthetic receptors are used in targeted gene therapies and fundamental research to investigate cell signalling, differentiation, migration, and morphogenesis [32] [33]. They can program engineered cells to self-organise into multicellular structures or pattern three-dimensional tissues. Synthetic receptor systems like LOCa can modulate aberrant self-renewal of hematopoietic stem cells and mitigate neurodegeneration in models of Alzheimer's disease [34]. Synthetic receptors can be partially or fully modular. Partially modular receptors retain the original sensor or actuator domain, while fully modular receptors have both engineered. Cell-surface receptors include enzyme-linked, G-protein-coupled, and ion channel-like receptors. [35].

Combining synthetic receptors and omics technologies offers unprecedented insights into cellular signalling, function, and disease. Techniques like TRAP enable targeted neuronal study based on activity, offering a dynamic approach to neural circuit research. [36]. Viral Tracers for Connectivity Mapping, both retrograde and anterograde, have been employed to map neural connections [16]. Integrating synthetic biology with single-cell analysis offers a comprehensive view of AD and enables targeted therapies. The E-SARE promoter shows higher reporter expression and dynamic range than natural IEG promoters. Combining synthetic promoters with omics technologies provides deeper insights into gene regulation and enables engineering new biological functions. [21].

Therapeutic strategies targeting astrocytes using Designer Receptors Exclusively Activated by Designer Drugs are being explored [35]. RNA sequencing can reveal changes in gene expression in response to DREADD-mediated neuronal activation or inhibition. The effects of astrocyte manipulation vary depending on the specific DREADD receptor used. Other factors include targeted brain region, timing of intervention, and the heterogeneity of astrocytes in different brain regions and disease conditions [37]. DREADDs control neuronal activity but don't directly reveal downstream molecular consequences. ATAC-seq reveals chromatin structure changes, indicating altered transcriptional regulation. Single-cell analysis informs cell-based therapies by identifying specific cell types for therapeutic agent delivery or immune modulation. [36].

3.3 Comprehensive Readout of Activity and Cell Type Markers (CRACK)

Combining transcriptomics, circuit tracing, and modulation offers a potent synthesis for studying disease-specific circuitry. Optogenetics and chemogenetics enable precise neural activity modulation and subsequent molecular characterization. Optogenetics uses light-sensitive proteins to control neural activity, providing precise manipulation of specific cell types or neural circuits. [38]. On the other hand, CRACK, chemogenetics, offers a less invasive method than optogenetics for altering neural activity in genetically defined neurons of animals [39]. CRACK technology combines population calcium imaging with multiplexed in situ hybridization. It creates brain-wide projections of identified cells and their behavioural tuning properties, enabling the study of specific circuit functions in AD. [11].

4. Advantages of Integrating Spatial Omics with Gene Circuit Technology

Spatial omics technologies offer unbiased spatial profiling of the transcriptome, revealing the operation of gene switches within the brain's complex tissue environment.

4.1 Context-Dependent Behaviour

Gene circuits modulate cellular function and adapt to regulatory networks. Circuit function varies with cellular context. Spatial omics reveal how circuit performance changes across cellular locations, enabling context-specific optimization. Amyloid plaques and tau tangles, AD hallmarks, vary across brain regions. Spatial omics unravel tissue heterogeneity and the spatial context of molecular components, aiding in optimizing synthetic biological systems for various applications. [2].

4.2 Off-Target Effects on Cellular Interactions

Spatial data enables effective gene switch design. Lysate-based cell-free systems (CFS) are valuable synthetic biology tools but lack living cell properties. Spatial omics visualizes circuit impact on gene expression, informing the development of more sophisticated gene circuit designs by identifying off-target effects.[40].

4.3 Predictability

In Alzheimer's, gene expression patterns likely change over time and across different brain regions as the disease progresses. Spatial transcriptomics coupled with time-series studies can help capture the spatiotemporal dynamics of gene regulation. However, ensuring the predictability of gene circuits remains a challenge, particularly for complex circuit functions [41]. Using orthogonal guide sequences, insulating DNA sequences, and whole-cell omics measurements can improve the predictability of gene circuits [42].

4.4 Resource Competition

Resource competition couplings pose a significant barrier to the successful engineering of cells across various organisms, including bacteria, fungi, and mammals [43]. This necessitates precise control and systematic modification of critical variables like recording environment shape and layout. Gene expression burden, diverting resources from natural functions, hinders cell growth and productivity. [44]. Spatial omics identifies areas of resource depletion due to circuit activity, optimizing circuit design. Identifying specific cell types and circuitry within the affected entorhinal-hippocampal system is crucial for developing targeted circuit therapies. [45]. Information theory assesses neural circuit pattern separation performance. Spatial omics reveals circuit effects on neighbouring genes, enabling disruption minimization. Gene-circuit approaches quantify stimulus or environmental shift scale changes through behavioural experiments [46].

4.5 Dynamic Process Control

Spatial transcriptomics will help study spatial and temporal selectivity governing diverse functions within the neocortex. For cell type-specific visualisation, the formation of learning-specific ephemeral and memory-specific enduring synapses utilising gene engineering techniques was demonstrated [47].

5. Future Directions

Multi-omics algorithms integrate genomic, proteomic, metabolomic, and other biological data to offer tailored AD management and functional recovery solutions. Fluorescence imaging of endogenous proteins, like PSD-95 in neurons using super-resolution techniques, is being developed. Combining molecular dynamics simulations with machine learning models offers comprehensive insights. Ion channels, complex proteins undergoing conformational changes upon activation, are challenging to model accurately. Cryo-EM provides detailed structural insights, improving computational model accuracy and drug design efforts. [48]. Predictive algorithms, powered by multi-omics data analysis, are revolutionising the field of rehabilitation and assistive systems. Bio Nexus Sentinel software platform integrates cytohistological RNA-seq and bioregulatory network exploration [49]. The patient-in-the-loop framework represents a unifying approach that can bridge the gap between computational modelling and clinical practice in neurorehabilitation. We can significantly enhance assistive augmentative rehabilitation by prioritising multidisciplinary collaboration and leveraging cutting edge research [50].

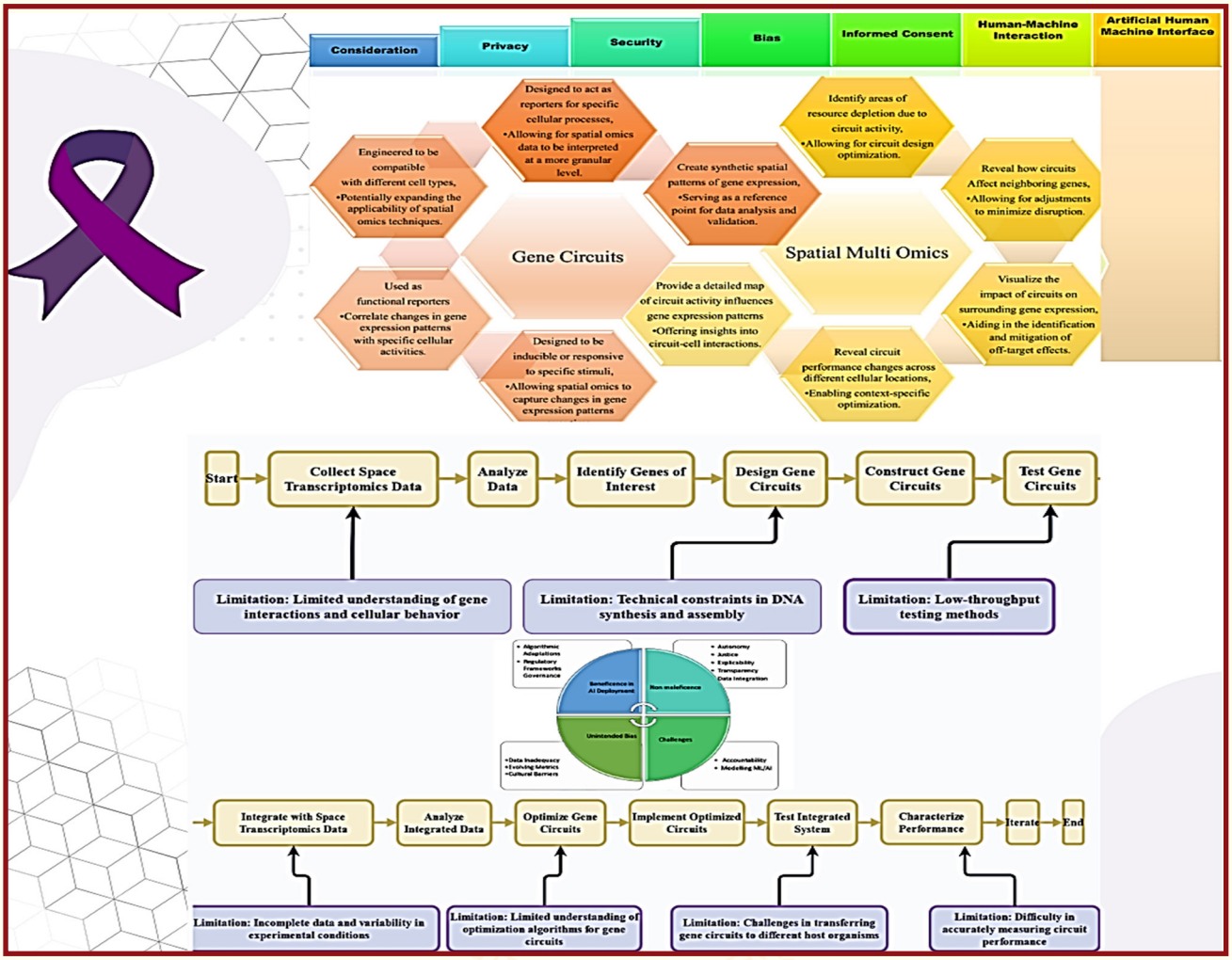


Figure 1. Synthetic Biology Solutions for Alzheimer's Disease: Technological Limitations and Ethical Challenges [created with Microsoft PowerPoint and Canva]

5.1 Microfluidic Technology

Organ-on-a-chip (OOC) technology is a cutting-edge innovation that simulates the functions and physiology of human organs on a microfluidic chip [51][52]. Microfluidic organ chips and OOCs create a controlled microenvironment that mimics factors like fluid flow, mechanical forces, and chemical gradients, which are crucial for maintaining cell function and behaviour [53]. Integrating single-cell transcriptomics and synthetic biology can advance in vitro systems using microfluidic chips to enhance understanding and drug development. Additionally, microfluidic platforms integrate various omics data, improving understanding of cellular heterogeneity and interactions within complex biological systems [54].

5.2 Organoids

Patient-derived organoids enable personalized treatment. Biomimetic scaffolds promote tissue healing and reduce inflammation. Advanced drug-delivery materials improve treatment. Brain organoids are used for toxicology, disease modelling, infection studies, personalized medicine, and gene-environment interaction studies. Organoids advance AD drug screening. Patient-derived organoid models investigate pathogenesis, guide clinical treatment, and facilitate drug screening. Stem cell-derived and biomimetic scaffold-based

organoids advance tissue engineering. Biomaterials create scaffolds for tissue regeneration. Multiomics and bioprinting evaluate pain medication efficacy and safety. Advanced imaging provides rich organoid information. Combining organoids and AI bridges experimental models and real-world clinical scenarios [55]. Omics and synthetic biology accelerate EV-based therapies. Digital microfluidics streamlines EV isolation for liquid biopsies.

5.3 Nanotechnology-based therapies

Nanotechnology strategies are discussed for enhancing drug delivery in brain disorders, including gene therapy, enzyme replacement therapy, and nano-assisted therapies like nano-immunotherapy and nano-gene therapy [56]. Successful drug discovery often requires the integration of various metal-based carriers and nanoparticles to reduce inflammation and pass through biological barriers and minimal systemic toxicity [57]. Nanotechnology, nanocarriers, nano immunotherapy and nano gold therapy improve drug delivery to specific sites, reducing systemic side effects [58].

5.4 Artificial Intelligence

The concept of Organoid Intelligence (OI) combines organoids with AI to model cognition and enable biological computing applications [59]. Computational techniques, such as virtual screening and molecular mechanics/dynamics simulations, enhance CAR-NK cell-based immunotherapy. Machine learning-based approaches target minimising collateral damage to healthy tissues, and optimise treatment protocols [60]. DeepD3 Framework is an open deep learning-based framework for quantifying dendritic spines in microscopy data, neural networks trained on data from different sources and experimental conditions [61]. Neuromorphic computing approaches can help identify patterns and make predictions beyond traditional methods' capability. By continuing to push the boundaries and fostering multidisciplinary integration, researchers can make significant strides towards conquering Alzheimer's disease.

6. Ethical Considerations

Recent advancements in transcriptomics and synthetic biology offer promising avenues for understanding and addressing AD. The multiomics and synthetic biology tools needs to address ethical considerations related to potential therapeutic applications. Careful monitoring and follow-up of patients in clinical trials are essential. Efforts should be made to ensure that these therapies are available to all patients who need them, regardless of their socioeconomic status.

- Off-target effects: Synthetic constructs may have unintended effects on other cellular processes or tissues. Thorough preclinical testing is crucial to minimise these risks.
- Immunogenicity: Engineered cells or gene therapies may trigger unwanted immune responses. Strategies to minimise immunogenicity has be developed [51][52]
- Informed Consent and Patient Autonomy: Synthetic biology is a complex field, and it may be difficult for patients to understand the risks and benefits of these therapies fully. Clear and accessible information should be provided to patients to ensure informed consent.

AD affects cognitive function, there are concerns about a patient's ability to provide informed consent, especially as the disease progresses. Several ethical principles are laid out to avoid any unintended outcomes of synthetic biology applications (Figure 1).

7. Conclusion

Alzheimer's disease is a complex neurodegenerative disorder characterised by progressive cognitive decline and memory loss. Transcriptomics, the study of gene expression, provides insights into the molecular mechanisms underlying AD. At the same time, synthetic biology enables the engineering of biological systems for therapeutic applications. Integrating spatial omics with synthetic gene circuit switches allows gene regulation

within tissues in spatial and temporal contexts. Integrating allows overcoming individual technological limitations to showcase tissue atlas, with the intricate interplay of genes across different cellular subregions. Gene circuits illuminate the function, and spatial omics pinpoint the differentially expressed genes underlying the observed patterns [62]

Genetic circuits and spatial omics complement each other to provide a detailed spatial-temporal map of gene expression patterns, offering novel insights into neuroscience. Combining these two fields allows us to understand AD pathogenesis better, identify novel therapeutic targets, and develop innovative treatment strategies.

Conflicts of Interest: There are no conflicts of interest to disclose.

Data Availability Statement: No new data were created during this study.

Data sharing: does not apply to this article.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable

References

1. Zhang Y, Chen H, Li R, Sterling K, Song W (2023) Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future. Sig Transduct Target Ther 8:1–26. https://doi.org/10.1038/s41392-023-01484-7
2. Park J, Kim J, Lewy T, Rice CM, Elemento O, Rendeiro AF, Mason CE (2022) Spatial omics technologies at multimodal and single cell/subcellular level. Genome Biol 23:1–19. https://doi.org/10.1186/s13059-022-02824-6
3. Zhang X, Lü P, Shen X (2022) Applications of single-cell multi-omics sequencing in deep understanding of brain diseases. Clinical and translational discovery. https://doi.org/10.1002/ctd2.95
4. Lebrigand K, Bergenstråhle J, Thrane K, Mollbrink A, Meletis K, Barbry P, Waldmann R, Lundeberg J (2023) The spatial landscape of gene expression isoforms in tissue sections. Nucleic Acids Res 51:e47. https://doi.org/10.1093/nar/gkad169
5. (2024) Spatial Gene Expression. In: 10x Genomics. https://www.10xgenomics.com/products/spatial-gene-expression
6. Vanrobaeys Y, Peterson ZJ, Walsh EN, Chatterjee S, Lin L-C, Lyons LC, Nickl-Jockschat T, Abel T (2023) Spatial transcriptomics reveals unique gene expression changes in different brain regions after sleep deprivation. Nat Commun 14:7095. https://doi.org/10.1038/s41467-023-42751-z
7. Hofbauer B, Zandawala M, Reinhard N, Rieger D, Werner C, Evers JF, Wegener C (2024) The neuropeptide pigment-dispersing factor signals independently of Bruchpilot-labelled active zones in daily remodelled terminals of Drosophila clock neurons. European Journal of Neuroscience. https://doi.org/10.1111/ejn.16294
8. Lim J, Souiki A, Ahmad P, Oomen CA, Huis in 't Veld G, Lansink CS, Pennartz CMA, Olcese U (2024) Transient DREADD manipulation of the dorsal Dentate Gyrus in rats impairs disambiguation of similar place-outcome associations. https://doi.org/10.1101/2024.02.20.581173
9. Albrecht A, Müller I, Weiglein A, Pollali E, Çalışkan G, Stork O (2022) Choosing memory retrieval strategies: A critical role for inhibition in the dentate gyrus. Neurobiology of Stress 20:100474. https://doi.org/10.1016/j.ynstr.2022.100474

10. Kiessling P, Kuppe C (2024) Spatial multi-omics: novel tools to study the complexity of cardiovascular diseases. Genome Med 16:1–17. https://doi.org/10.1186/s13073-024-01282-y

11. Grieco SF, Holmes TC, Xu X (2023) Probing neural circuit mechanisms in Alzheimer's disease using novel technologies. Mol Psychiatry 28:4407–4420. https://doi.org/10.1038/s41380-023-02018-x

12. Igarashi KM (2022) Entorhinal cortex dysfunction in Alzheimer's disease. Trends in Neurosciences 46:124–136. https://doi.org/10.1016/j.tins.2022.11.006

13. Jagtap S, Pirayre A, Bidard F, Duval L, Malliaros FD (2022) BRANEnet: embedding multilayer networks for omics data integration. BMC Bioinformatics 23:429. https://doi.org/10.1186/s12859-022-04955-w

14. Du P, Lou C, Zhao X, Wang Q, Ji X, Wei W (2021) CRISPR-Based Genetic Switches and Other Complex Circuits: Research and Application. Life 11:1255. https://doi.org/10.3390/life11111255

15. Bouin A, Wu G, Koyuncu OO, Ye Q, Kim K-Y, Wu MY, Tong L, Chen L, Phan S, Mackey MR, Ramachandra R, Ellisman MH, Holmes TC, Semler BL, Xu X (2024) New rabies viral resources for multi-scale neural circuit mapping. Molecular Psychiatry 1–17. https://doi.org/10.1038/s41380-024-02451-6

16. Du W, Li E, Guo J, Arano R, Kim Y, Chen Y-T, Thompson A, Oh SJ, Samuel A, Li Y, Oyibo HK, Xu W (2023) Directed stepwise tracing of polysynaptic neuronal circuits with replication-deficient pseudorabies virus. Cell Rep Methods 3:100506. https://doi.org/10.1016/j.crmeth.2023.100506

17. Zhang Q, Li T, Xu M, Islam B, Wang J (2024) Application of Optogenetics in Neurodegenerative Diseases. Cell Mol Neurobiol 44:57. https://doi.org/10.1007/s10571-024-01486-1

18. Swanson JL, Chin P-S, Romero JM, Srivastava S, Ortiz-Guzman J, Hunt PJ, Arenkiel BR (2022) Advancements in the Quest to Map, Monitor, and Manipulate Neural Circuitry. Frontiers in Neural Circuits 16:886302. https://doi.org/10.3389/fncir.2022.886302

19. Zhu D, Johnson HJ, Chen J, Schaffer DV (2022) Optogenetic Application to Investigating Cell Behavior and Neurological Disease. Frontiers in Cellular Neuroscience 16:811493. https://doi.org/10.3389/fncel.2022.811493

20. Benisch M, Aoki SK, Khammash M (2023) Unlocking the potential of optogenetics in microbial applications. Current Opinion in Microbiology 77:102404. https://doi.org/10.1016/j.mib.2023.102404

21. Pang B, Wu X, Chen H, Yan Y, Du Z, Yu Z, Yang X, Wang W, Lu K (2024) Exploring the memory: existing activity-dependent tools to tag and manipulate engram cells. Frontiers in Cellular Neuroscience 17:1279032. https://doi.org/10.3389/fncel.2023.1279032

22. Xu P, Peng J, Yuan T, Chen Z, He H, Wu Z, Li T, Li X, Wang L, Gao L, Yan J, Wei W, Li CT, Luo Z-G, Chen Y (2024) High-throughput mapping of single-neuron projection and molecular features by retrograde barcoded labeling. eLife 13:e85419. https://doi.org/10.7554/elife.85419

23. Yang F, Zhao Z, Zhang D, Xiong Y, Dong X, Wang Y, Yang M, Pan T, Liu C, Liu K, Lin Y, Liu Y, Tu Q, Dang Y, Xia M, Mi D, Zhou W, Xu Z (2024) Single-cell multi-omics analysis of lineage development and spatial organization in the human fetal cerebellum. Cell Discovery 10:22. https://doi.org/10.1038/s41421-024-00656-1

24. Gao M-Y, Wang J-Q, He J, Gao R, Zhang Y, Li X (2023) Single-Cell RNA-Sequencing in Astrocyte Development, Heterogeneity, and Disease. Cellular and Molecular Neurobiology 43:3449–3464. https://doi.org/10.1007/s10571-023-01397-7

25. Shi Y, Huang L, Dong H, Yang M, Ding W, Zhou X, Lu T, Liu Z, Zhou X, Wang M, Zeng B, Sun Y, Zhong S, Wang B, Wang W, Yin C, Wang X, Wu Q (2024) Decoding the spatiotemporal regulation of transcription factors during human spinal cord development. Cell Research 34:193–213. https://doi.org/10.1038/s41422-023-00897-x

26. (2024) nCounter® Analysis Systems for Biomarker Validation and Biomarker Development. In: NanoString. https://nanostring.com/products/ncounter-analysis-system/ncounter-systems-overview/

27. Cs C, J X, Y S, Sr P, Je H, M K, G J, Hm K, Jh L (2021) Microscopic examination of spatial transcriptome using Seq-Scope. Cell 184:. https://doi.org/10.1016/j.cell.2021.05.010

28. Siddiqui M, Tous C, Wong WW (2022) Small molecule-inducible gene regulatory systems in mammalian cells: progress and design principles. Current Opinion in Biotechnology 78:102823. https://doi.org/10.1016/j.copbio.2022.102823

29. Eisenhut P, Marx N, Borsi G, Papež M, Ruggeri C, Baumann M, Borth N (2024) Manipulating gene expression levels in mammalian cell factories: An outline of synthetic molecular toolboxes to achieve multiplexed control. New Biotechnology 79:1–19. https://doi.org/10.1016/j.nbt.2023.11.003

30. Barbier I, Kusumawardhani H, Chauhan L, Harlapur PV, Jolly MK, Schaerli Y (2023) Synthetic Gene Circuits Combining CRISPR Interference and CRISPR Activation in E. coli: Importance of Equal Guide RNA Binding Affinities to Avoid Context-Dependent Effects. ACS Synth Biol 12:3064–3071. https://doi.org/10.1021/acssynbio.3c00375

31. Kraus C, Sontheimer EJ (2023) Applications of Anti-CRISPR Proteins in Genome Editing and Biotechnology. Journal of Molecular Biology 435:168120. https://doi.org/10.1016/j.jmb.2023.168120

32. Chen WCW, Gaidukov L, Lai Y, Wu M-R, Cao J, Gutbrod MJ, Choi GCG, Utomo RP, Chen Y-C, Wroblewska L, Kellis M, Zhang L, Weiss R, Lu TK (2022) A synthetic transcription platform for programmable gene expression in mammalian cells. Nat Commun 13:6167. https://doi.org/10.1038/s41467-022-33287-9

33. Rajasekaran R, Chang C-C, Weix EWZ, Galateo TM, Coyle SM (2024) A programmable reaction-diffusion system for spatiotemporal cell signaling circuit design. Cell 187:345-359.e16. https://doi.org/10.1016/j.cell.2023.12.007

34. Teng F, Cui T, Zhou L, Gao Q, Zhou Q, Li W (2024) Programmable synthetic receptors: the next-generation of cell and gene therapies. Signal Transduction and Targeted Therapy 9:7. https://doi.org/10.1038/s41392-023-01680-5

35. Lee H-G, Wheeler MA, Quintana FJ (2022) Function and therapeutic value of astrocytes in neurological diseases. Nat Rev Drug Discov 21:339–358. https://doi.org/10.1038/s41573-022-00390-x

36. Kim D, Tran A, Kim HJ, Lin Y, Yang JYH, Yang P (2023) Gene regulatory network reconstruction: harnessing the power of single-cell multi-omic data. npj Syst Biol Appl 9:1–13. https://doi.org/10.1038/s41540-023-00312-6

37. Pereira MJ, Ayana R, Holt MG, Arckens L (2023) Chemogenetic manipulation of astrocyte activity at the synapse— a gateway to manage brain disease. Front Cell Dev Biol 11:. https://doi.org/10.3389/fcell.2023.1193130

38. Ördög B, De Coster T, Dekker SO, Bart CI, Zhang J, Boink GJJ, Bax WH, Deng S, den Ouden BL, de Vries AAF, Pijnappels DA (2023) Opto-electronic feedback control of membrane potential for real-time control of action potentials. Cell Rep Methods 3:100671. https://doi.org/10.1016/j.crmeth.2023.100671

39. Tan P, He L, Huang Y, Zhou Y (2022) Optophysiology: Illuminating cell physiology with optogenetics. Physiol Rev 102:1263–1325. https://doi.org/10.1152/physrev.00021.2021

40. Wagner L, Jules M, Borkowski O (2023) What remains from living cells in bacterial lysate-based cell-free systems. Computational and Structural Biotechnology Journal 21:3173–3182. https://doi.org/10.1016/j.csbj.2023.05.025

41. Şimşek E, Yao Y, Lee D, You L (2022) Toward predictive engineering of gene circuits. Trends in Biotechnology 41:760–768. https://doi.org/10.1016/j.tibtech.2022.11.001

42. Dwijayanti A, Zhang C, Poh CL, Lautier T (2022) Toward Multiplexed Optogenetic Circuits. Frontiers in Bioengineering and Biotechnology 9:

43. McBride CD, Grunberg TW, Del Vecchio D (2021) Design of genetic circuits that are robust to resource competition. Current Opinion in Systems Biology 28:100357. https://doi.org/10.1016/j.coisb.2021.100357

44. Sequeiros C, Vázquez C, Banga JR, Otero-Muras I (2023) Automated Design of Synthetic Gene Circuits in the Presence of Molecular Noise. ACS Synthetic Biology 12:2865–2876. https://doi.org/10.1021/acssynbio.3c00033

45. Borzello M, Ramirez S, Treves A, Lee I, Scharfman H, Stark C, Knierim JJ, Rangel LM (2023) Assessments of dentate gyrus function: discoveries and debates. Nat Rev Neurosci 24:502–517. https://doi.org/10.1038/s41583-023-00710-z

46. Wang M, Song W-M, Ming C, Wang Q, Zhou X, Xu P, Krek A, Yoon Y-J, Ho L, Orr ME, Yuan G-C, Zhang B (2022) Guidelines for bioinformatics of single-cell sequencing data analysis in Alzheimer's disease: review, recommendation, implementation and application. Molecular Neurodegeneration. https://doi.org/10.1186/s13024-022-00517-z

47. Severino L, Kim J, Nam M-H, McHugh TJ (2024) From synapses to circuits: What mouse models have taught us about how autism spectrum disorder impacts hippocampal function. Neuroscience & Biobehavioral Reviews 158:105559. https://doi.org/10.1016/j.neubiorev.2024.105559

48. Torres R, Thal LB, McBride JR, Cohen BE, Rosenthal SJ (2024) Quantum Dot Fluorescent Imaging: Using Atomic Structure Correlation Studies to Improve Photophysical Properties. The Journal of Physical Chemistry C 128:3632–3640. https://doi.org/10.1021/acs.jpcc.3c07367

49. Matzko RO, Konur S (2024) BioNexusSentinel: a visual tool for bioregulatory network and cytohistological RNA-Seq genetic expression profiling within the context of multicellular simulation research using ChatGPT-Augmented software engineering. Bioinformatics Advances vbae046. https://doi.org/10.1093/bioadv/vbae046

50. Cashaback JGA, Allen JL, Chou AH-Y, Lin DJ, Price MA, Secerovic NK, Song S, Zhang H, Miller HL (2024) NSF DARE—transforming modeling in neurorehabilitation: a patient-in-the-loop framework. Journal of NeuroEngineering and Rehabilitation 21:23. https://doi.org/10.1186/s12984-024-01318-9

51. Dijk G, Poulkouras R, O'Connor RP (2022) Electroporation Microchip With Integrated Conducting Polymer Electrode Array for Highly Sensitive Impedance Measurement. IEEE Transactions on Biomedical Engineering 69:2363–2369. https://doi.org/10.1109/tbme.2022.3143542

52. Habibey R, Arias JER, Striebel J, Busskamp V (2022) Microfluidics for Neuronal Cell and Circuit Engineering. Chemical Reviews 122:14842–14880. https://doi.org/10.1021/acs.chemrev.2c00212

53. Sharkey C, White R, Finocchiaro M, Thomas J, Estevam J, Konry T (2024) Advancing Point-of-Care Applications with Droplet Microfluidics: From Single-Cell to Multicellular Analysis. Annual Review of Biomedical Engineering 26:. https://doi.org/10.1146/annurev-bioeng-110222-102142

54. Yang N, Sun C, Dong C, Huang Y, Zhu Y, Gu Z (2024) Emerging microfluidics for the modeling and treatment of arthritis. Engineered Regeneration 5:153–169. https://doi.org/10.1016/j.engreg.2024.02.002

55. Patel D, Shetty S, Acha C, Pantoja IEM, Zhao A, George D, Gracias DH (2024) Microinstrumentation for Brain Organoids. Advanced Healthcare Materials e2302456. https://doi.org/10.1002/adhm.202302456

56. Dong H, Lin J, Tao Y, Jia Y, Sun L, Li WJ, Sun H (2024) AI-enhanced biomedical micro/nanorobots in microfluidics. Lab on a Chip 24:1419–1440. https://doi.org/10.1039/d3lc00909b

57. Singh S, Sharma K, Sharma H (2024) Green Extracts with Metal-based Nanoparticles for Treating Inflammatory Diseases: A Review. Current Drug Delivery 21:544–570. https://doi.org/10.2174/1567201820666230602164325

58. 58. Kumar PPP, Mahajan R (2024) Gold Polymer Nanomaterials: A Promising Approach for Enhanced Biomolecular Imaging. Nanotheranostics 8:64–89. https://doi.org/10.7150/ntno.89087

59. Hartung T, Pantoja IEM, Smirnova L (2024) Brain organoids and organoid intelligence from ethical, legal, and social points of view. Frontiers in Artificial Intelligence 6:1307613. https://doi.org/10.3389/

frai.2023.1307613

60. Amaya-Rodriguez CA, Carvajal-Zamorano K, Bustos D, Alegría-Arcos M, Castillo K (2024) A journey from molecule to physiology and in silico tools for drug discovery targeting the transient receptor potential vanilloid type 1 (TRPV1) channel. Frontiers in Pharmacology 14:1251061. https://doi.org/10.3389/fphar.2023.1251061
61. Mahendrakar P, kumar D, Patil U (2024) A Comprehensive Review on MRI-based Knee Joint Segmentation and Analysis Techniques. Current Medical Imaging 20:e150523216894. https://doi.org/10.2174/1573405620666230515090557
62. Greiss F, Lardon N, Schütz L, Barak Y, Daube SS, Weinhold E, Noireaux V, Bar-Ziv R (2024) A genetic circuit on a single DNA molecule as an autonomous dissipative nanodevice. Nature communications 15:883. https://doi.org/10.1038/s41467-024-45186-2

Opinion/Viewpoint

Karma as a Non-religious Scientific Concept

Sudarshan K. Suneja, MD, Ph.D.

Diplomate, American Board of Psychiatry and Neurology; Visiting Professor,

Sri Madhusudan Sai Institute for Medical Sciences & Research (SMSIMSR).

Correspondence: sunejabooks@gmail.com Tel.: (+1-314-495-7212)

Keywords: karma; laws of karma; human destiny; spirituality; reincarnation

The concept of Karma is very practical, useful, and empowering concept, though it is also widely misunderstood. One common misunderstanding is that it is a religious concept belonging to Hindu religion. However, the perspective that Karma is actually a scientific concept needs to be recognized. To understand its scientific basis, we have to understand how the concept of Karma was originally developed.

Ancient thinkers and philosophers in India came up with this concept, most likely, to explain the seemingly inexplicable happenings in human life. In order to understand how this happened, we have to transport ourselves back in time to before 1500 BCE. Ancient humans observed that every action results in a corresponding outcome, conceptually similar to Newton's third law of motion – namely, that every action has an equal and opposite reaction [1]. This was evident from the day-to-day happenings in their lives. Some of these outcomes could be easily explained as to why they happened in reference to immediate past actions. For example, if a person ate more than his gastric capacity, he would vomit soon after eating. So, his vomiting would be easily explained as a result of overeating.

But some events happened which could not be explained when they looked at immediate past behaviors but could be explained when they looked at recent past actions. For example, if a person vomited today, they did not find anything in his same-day actions that could cause him to vomit. But when they looked at his behaviors in the previous couple of days, they may find that the person ate food that had gone bad because it was stale, contaminated, or spoiled. So, previous action of two days ago could explain today's outcome of vomiting. Generally, food poisoning due to eating spoilt or contaminated food takes several hours to show its effect because the bacteria contaminating the food need several hours to release enough toxins that cause vomiting or other problems.

And sometimes things happened which could not be explained even when they looked at recent past behaviors. For example, if a person vomited today and they looked at his actions from the recent past, they did not find anything that could cause vomiting. However, if they looked at his behaviors over the

Citation: Suneja S. K.; *Awareness* 2(1): 21-24.

Academic Editor: Dr. K.J.S. Anand

Received: Dec. 19, 2024

Revised: Dec. 21,2024

Accepted: Dec. 23,2024

Published: Jan. 14, 2025

last six months to a year, they may find that the person was eating a particular poisonous herb in small quantities for a long period which slowly accumulated in his body and ultimately lead to vomiting. Thus, his behaviors over the past one year could explain today's outcome of vomiting.

Thus, commonly the current happenings could be explained as they expanded their time horizon. For example, if a person develops clogged arteries of the heart, that did not happen because the person ate fatty foods and did not engage in any physical exercise for the past one week or one month or even one year. But it can happen because of lifestyle habits for the last 10 or 20 or even 30 years. This is because the process of clogging of arteries is very slow and it generally takes several years to develop to a level where it can cause a heart attack or other physical problems.

But sometimes it so happened that the current event could not be explained even if they looked at an entire lifetime of behaviors. For example, if a person developed cancer of the stomach, they could not explain it by his behavior in this life. Somebody may think that this person ate too much spicy food but then there are thousands of other people who ate similarly, if not more, spicy foods but they did not develop stomach cancer. So most likely there were some behaviors or actions by that person before his current life in his previous life which are contributing to the outcome of cancer in this life. To refer to those actions done in the previous life and to distinguish them from the actions done in this life, they coined the term 'Karma'. Thus, the word Karma helped in two ways: First, whenever they used the word Karma, it automatically meant the actions undertaken in a previous life. Secondly, this word helped in the communication process. For example, instead of saying "actions done in a previous life" they simply had to use only one word 'Karma'. Going back to our example of cancer, you may ask how did the past Karmas done in a previous life contribute to cancer in this life? We will soon come back to this question, but first, those scientists who remain unconvinced about transmigration of the soul across multiple lifetimes may need to seriously consider their position based on the following statements:

Plotinus (AD 205-270) has this to say about transmigration of the soul, *"The human soul is part of the world soul. It turned towards matter and fell from the spiritual state. It must struggle to free itself from the bondage of matter. If it fails, it enters other bodies after death. It passes through a series of births and deaths until it is entirely freed of all material impurity. When purification is attained through various forms of discipline, the soul unites with the world soul and ultimately with the God-head."*

Even the original Bible contained several thoughts and passages on reincarnation and transmigration of the soul. But Christian theologian leaders who met in A.D. 543, at the Quincentennial Council of Christianity in Constantinople, decided to expunge them from the Bible with the following injunction, *"If anyone maintains the legendary pre-existence of souls and the monstrous idea of restitution, let him be anathema."* Such excised passages are still preserved in the Vatican Apostolic Library in Rome and may become available to authorized Biblical scholars.

Thomas Huxley, (1825-1895), a relatively modern scholar, has made the following observations on this theme, *"every sentient being is reaping what it has sown, if not in this life then in one or other of the infinite series of antecedent existence of itself..... like the theory of evolution, it is based on reality."*

Ralph Waldo Emerson (1803–1882), another great American thinker, has said, *"There are stairs below us and stairs above…"*, whereas Walt Whitman Jr. (1819-1892) also comments, *"No doubt I have died myself ten thousand times before."* The rhymes of a famous English poet, William Wordsworth (1770-1850) are often quoted:

"Our birth is but a sleep and a forgetting

The Soul that rises with us, our life's staff

Hath had elsewhere its setting....."

An ancient Iranian poet, Maulana Roumi, who was the disciple of his great master, Shams-i-Tabrīzī or Shams al-Din Mohammad (1185–1248), is considered a great Sufi saint of Islam and his verses are found in many books on Sufi thought and mysticism:

"I died as mineral and became a plant

I died as plant and rose to be animal

I died as animal and I was man

Why should I fear? When was I less by dying?

Yet, once more I shall die as man to soar

With angels blessed, but even from angelhood I must pass on

All except God doth perish.

When I have sacrificed my angelhood

I shall become what no mind ever conceived

Oh! let me not exist. For non-existence proclaims in organ tones

To HIM we shall return."

Scientific proof for transmigration of the soul has been amply demonstrated through the meticulous research observations of a well-known psychotherapist, Dr. Brian Weiss, Chairman Emeritus of Psychiatry at the Mount Sinai Medical Center in Miami. He wrote several books titled: *"Many Lives, Many Masters"*; *"Same Soul, Many Bodies"*; *"Only Love is Real"*; and *"Through Time Into Healing"*. Similar observations were corroborated by several modern scientists in our current times, eliminating the last vestiges of doubt or dogma related to transmigration of the soul.

Against this backdrop, it is easy to understand that our past Karmas determine the parents assigned to us in this life because we are born to those persons with whom we have a lot of Karmas in common as explained in Karmic Law #33 [see ref. 2]. Since we inherit our genes from our parents, therefore if we could inherit a gene with stomach cancer susceptibility, then we are more likely to develop stomach cancer in this life if we eat spicy foods for a long time. Thus, the occurrence of stomach cancer in this life, which could not be explained even when we looked at lifelong behaviors in this life, was explained when we looked at the actions or Karmas done in a previous life. This is an example of how, when we broaden our time horizon enough, we can get closer to the truth.

The concept of Karma was developed and introduced in the thought process thousands of years ago in India and since then it has been able to explain the seemingly inexplicable happenings in the lives of millions of people and often alleviate their mental stress and agony. When we look at how this concept was developed in a logical manner, a few observations are worth mentioning:

1. The concept of Karma was developed by the scholarly philosophers and thinkers in ancient times and not by religious or spiritual leaders. Thus, the concept of Karma is originally a scholarly concept and not a religious or spiritual concept. But later on, it was presented as a religious or spiritual concept, resulting in the widely-held misconception. Since this concept originated in India and *Sanathana Dharma* was the predominant religion in India at that time, so these thinkers and philosophers happened to follow the most prevalent religion. People worldwide now think that Karma is a Hindu concept and it belongs to Hindu religion which is not correct.
2. The concept of Karma is not an empirical concept, and it was not empirically conceived by a random person without any logic or reasoning. As explained above, it was developed after rigorous observation and scientific thinking by the most brilliant thinkers of that time. Thus, it is a rigorous scientific concept, in the strictest sense of that term. By the term "scientific", I mean systematic, organized, logical, and open-minded which meets the most rigorous definition of "scientific" in the present times.

3. The concept of Karma developed thousands of years ago has helped to alleviate the distress and mental agony of millions of people by providing them a logical explanation for the problematic happenings in their lives which cannot be explained by any other means. Some examples of these problematic events can be illustrated in the following questions:

    a. Why does one newborn child have heart disease at birth while another child does not?

    b. Why does a particular treatment work for one patient but not for another patient with the same problem?

    c. Why is there so much inequality in the world, such as disparity between the rich and the poor?

    d. Why is it that some people who are doing bad things like cheating and lying all the time are flourishing and good people who are always helpful to others and are honest are doing poorly?

As described before [3], these questions are not meant to discourage the reader to be resigned to one's so-called fate, because in fact, according to the laws of Karma, we all have the ability to improve, or perhaps even eradicate the consequences of our past Karmas. This is the empowering aspect of Karma.

Supplementary Materials: None.

Author Contributions: Dr. S.K. Suneja .

Funding: None.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable

Acknowledgments: The author is grateful for the spiritual guidance and teachings of Sri Sathya Sai Baba and Sri Madhusudan Sai.

Conflicts of Interest: None.

References

1. Isaac Newton. Philosophiæ Naturalis Principia Mathematica (Mathematical Principles of Natural Philosophy). Edmund Halley, publisher for The Royal Society, London, (UK); 1687.
2. Suneja, S. K. 9 Proven Laws of Reincarnation: How to use them to Craft Your Destiny. (2nd Edition, Updated 2024). KDP Publishing www.amazon.com, Seattle WA, USA; 2021a.
3. Suneja, S. K. 36 Powerful Laws of Karma: The Secrets of Karmic Code Explained First Time. (2nd Edition, Updated 2024). KDP Publishing www.amazon.com, Seattle WA, USA; 2021b.

Perspective

Congenital heart defects in Down's Syndrome: *Identification of a unique molecular signature*

Nallur B. Ramachandra, Ph.D.

DAE-Raja Ramanna Chair, Department of Studies in Genetics and Genomics, University of Mysore, Mysore, India

Correspondence: nallurbr@gmail.com; ramachandra@genetics.uni-mysore.ac.in. Tel.: +91 9880033687

Abstract: Congenital heart defects (CHD) are seen frequently in about 50% of patients with Down's syndrome (DS) and are the leading cause of death of DS in the early years of life. Recently, Lana-Elola et al. [1], in their seminal research article, showed that heart tissue from human fetuses with DS has characteristic transcriptional changes, as that of the embryonic hearts from the Dp1Tyb and Dp3Tyb mice models of DS that show CHD. They demonstrated that one of the causative genes for CHD in DS is *Dyrk1a*. They showed that an increased dosage of *Dyrk1a* results in impaired cell proliferation and mitochondrial respiration of cardiomyocytes and is necessary to cause CHD in DS. They reversed the CHD phenotype in Dp1Tyb mouse by reducing the copy number of *Dyrk1a* to two or inhibiting this gene expression.

Keywords: Congenital heart defects, Down's syndrome, mouse model, human heart, *Dyrk1a* gene, Notch signaling

Citation: Nallur B. R.; *Awareness*, 2 (1): 25-29

Academic Editor: Dr. B.K. Thelma.

Received: Oct. 21,2024

Revised: Dec. 17, 2024

Accepted: Dec 19, 2024

Published: Jan. 14, 2025

1. Introduction

In 1866, John Langdon Down described a slightly flattened facial profile, an upward slant to the eyes, low muscle tone, mental retardation and a single deep crease across the palm as the characteristic features of Down's syndrome (DS) [2]. DS is a common genetic condition and the most frequent cause of genetic mental retardation occurring in one out of every 700 newborns across all racial and economic groups [2]. Congenital heart defects (CHD) are seen frequently in about 50% of patients with DS and are the leading cause of death of DS in the early years of life [3-4]. Even 65 years after the discovery of Trisomy-21 in DS, chronic health issues and medical care of DS patients remain limited, resulting in premature deaths or mortality. With the advent of genomics technology, a wealth of new individualized information and diagnostics are possible, facilitating personalized treatments and predicting future risk factors for each individual. A seminal study by Lana-Elola et al., [1] identified the over-expression of the Dyrk1a gene in mice models of DS, which is responsible for the manifestation of CHD in DS. Here, their investigations and implications of their findings for possible treatments for DS are outlined.

1.1. Discovery of Trisomy-21 and risk factors for DS

After elucidating human chromosome number 2n=46 [5], Lejeune et al., [6] discovered the presence of an extra chromosome 21 in DS subjects through karyotypic analysis. Karyotypic analysis became the routine prenatal diagnostic test to confirm trisomy-21 in suspected DS fetuses. Subsequent studies found that chromosomes 21q21 to 21q22.3 form the critical DS region that causes most DS phenotypes [7]. The additional copy of chromosome 21 was seen in the abnormal eggs of mothers over 35 years of age [8], although the mother's lifestyle, environment, and occupational exposures may surpass maternal age as risk factors for chromosome nondisjunction leading to trisomy-21 [9].

Further karyotypic and fluorescence *in situ* hybridization analyses revealed that DS can be seen chromosomally as free trisomy (92-95%), translocation trisomy-21 (3-4%) and mosaic trisomy-21 (2-4%) [10]. A well-established precursor for trisomy-21 is meiotic nondisjunction, leading to abnormal segregation of chromosomes during gametogenesis in older mothers [11]. However, we have reported a contrasting trend where more DS children are born to younger mothers aged 18-29 years in India than to older mothers [12]. We found that younger mothers born to their mothers at the age of above 30 years produced more DS children. Therefore, besides the known risk factors, the maternal grandmother's age at the time of birth of the mother is a risk factor for DS [12].

1.2. Genes on chromosome 21

The Human Genome Project launched in October 1990 revealed that the average human genome is 3.2 billion bases per haploid set, encoding approximately 25,000 protein-coding genes. Further, chromosome 21 has about 329 genes with a size of 48 Mb [2]. This investigation opened the door for more significant advances in DS research. The over-expression of the genes in trisomy-21 is a challenge in understanding gene functions and interpreting biological characteristics. Gardiner et al., [13] reported that about 170 genes from chromosome 21 encode open reading frames conserved in orthologous regions of mouse chromosomes 16, 17 and 10. This has led to the development of mouse models to unravel the genotype-phenotype correlations in DS effectively.

2. Genes identified for DS-associated CHD

The development of the human heart is a complex process; any deviation can lead to CHD. In India and worldwide, the incidence of CHD exceeds 2% of all live-births globally [14-16]. CHD affects nearly 50% in babies with DS born with a partial or complete extra copy of chromosome 21 [4]. Over the years, Lana-Elola and colleagues have attempted to map the genetic determinants of CHD on chromosome 21 using human samples and mice models. They genetically engineered a mouse model, Dp1Tyb, with extra copies of 145 coding genes on mouse chromosome 16, corresponding to about 60% of the human chromosome 21, which exhibits a broad range of DS-like phenotypes. Lana-Elola et al., [1] further demonstrated that in embryonic DS mice models, three instead of the normal two copies of the dual-specificity tyrosine phosphorylation–regulated kinase 1A (Dyrk1a) gene caused the cardiac pathology as outlined below.

These investigators employed embryonic DS mice models and human fetal heart tissue with DS, RNA sequencing, high-resolution episcopic microscopy imaging and 3D modelling to correlate the dose-sensitive expression of Dyrk1a with CHD phenotype, as well as changes in mitochondrial function and cell proliferation in the Dp1Tyb mouse. RNA sequencing analysis in Dp1Tyb mouse embryonic hearts, human DS hearts and also hearts of Dp3Tyb mouse strain having an extra copy of 39 protein-coding genes contained within the large duplication showed similar rates of CHD, indicating that these 39 genes were sufficient to cause CHD, associated with decreased expression of oxidative phosphorylation genes, which are correlated with CHD.

The Ts1Rhr mouse embryos have an extra copy of a slightly shorter region containing just 31 genes and they do not show CHD. The decreased expression of three proliferation gene sets was seen in Dp3Tyb mouse hearts, but only two of these were also decreased in Ts1Rhr mouse hearts. These findings suggest that impaired oxidative phosphorylation and potentially cellular proliferation may contribute to the etiology of CHD. Single-cell RNA sequence analysis revealed similar gene expression changes across Dp1Tyb mouse

embryonic heart cell types. The transcriptomics of human DS fetal hearts and mouse embryonic hearts from the DS mouse models showed that reduced expression of mitochondrial respiration genes and cell proliferation genes were correlated with CHD pathology. Flow cytometric analysis of Dp1Tyb mouse hearts showed an increased proportion of cardiomyocytes and endocardial cells in the G1 phase and fewer cells in the S phase of cell division, indicating that embryonic cardiomyocytes have defective mitochondria with reduced basal and maximal respiration rates consistent with impaired mitochondrial function.

Genetic crosses between the Dp1Tyb mouse model and mice strains deficient in each of the 39 candidate genes were conducted using a systematic genetic mapping approach. They observed that reduced copy number of dual-specificity tyrosine phosphorylation–regulated kinase 1A (Dyrk1a) gene from three to two completely rescued CHD indicating that three copies of Dyrk1a are necessary to cause CHD in the Dp1Tyb mouse [1-4]. An increased dosage of Dyrk1a causes key transcriptional changes in Dp1Tyb embryonic hearts. Dyrk1a is also broadly expressed in many cardiac cell types, indicating its role in causing the observed changes in cellular pathways leading to CHD. The hearts from human DS, Dp1Tyb, and Dp3Tyb mice also showed decreased expression of proliferation genes partially correlated with CHD.

Further, the reduction of phosphorylated retinoblastoma protein in Dp1Tyb mouse embryonic hearts was reversed by reducing the copy number of Dyrk1a from three to two and less expression of E2F-regulated genes that are required for the G1 to S phase transition, indicating that three copies of Dyrk1a can lead to mitochondrial dysfunction in embryonic cardiomyocytes. This suggests that an increased dosage of DYRK1A protein resulted in impairment of mitochondrial function and CHD pathology in the Dp1Tyb mouse. Pharmacological inhibition of DYRK1A also resulted in partially rescuing the DYRK1A-dependent CHD in Dp1Tyb embryos. Taken together, the findings demonstrate that the three copies of the Dyrk1a gene contribute to CHD in the Dp1Tyb mouse. This study adds to the growing literature on the genes and gene networks responsible for causing CHD in humans, similar to the abnormalities in embryonic Notch 1 signaling, explaining bicuspid aortic valve, or aortic stenosis, or hypoplastic left heart syndrome [17] or other genetic causes of obstructive left-heart lesions [18]..

3. Limitations and Future Directions

Although extensive investigations have been done to explain the three copies of Dyrk1a cause CHD, this study has several limitations. Firstly, it is unclear how defects in mitochondrial function and proliferation in most cardiac cells can cause localized defects in septation rather than broader cardiomyopathy. Further study is needed to understand the developmental defects in Dp1Tyb mouse hearts that may lead to ventricular and atrioventricular septal defects. Secondly, even though an increased dosage of Dyrk1a is necessary, it may be insufficient to cause mitochondrial defects and CHD; therefore, other genes associated with CHD phenotypes in DS need to be explored. Thirdly, DYRK1A phosphorylates many proteins that regulate transcription, splicing, and apoptosis. Further studies are needed to determine whether any of these DYRK1A targets are involved in DYRK1A-induced CHD, and why the inhibitor Leucettinib-21 does not have a more substantial effect on transcriptional changes in Dp1Tyb embryos? Further studies are needed to explore the cardiac pathology resulting from a complex genetic interplay between Dyrk1a and other unknown causative genes, the association of Dyrk1a with other known DS features such as neurodevelopment deficits [19].

4. Conclusions

Despite 65 years having passed since the discovery of the origin of Trisomy-21, DS patients continue to suffer from the consequences of this chromosomal anomaly. The extra free copy of chromosome 21 creates a remarkable change in the genome of the DS subjects to produce distinct phenotypes, including 50% of them suffering from CHD. However, it is noteworthy that advanced technology in this millennium is the most exciting time for investigating human genetic diseases, including DS. Although an extra copy of Dyrk1a was associated with heart defects in mouse, its contribution to human heart defects is yet to be fully explored. The

systematic genetic mapping approach for dosage-sensitive genes can be used to identify causative genes and mechanisms responsible for the many other phenotypes of DS. Further, identifying all the causative genes and their inhibitors would help study the pathological mechanisms for CHD that can be potential therapeutic targets for treating DS-associated heart defects, which is essential for most DS clinical conditions. Further research into the genetic and molecular basis of Trisomy-21 promises to transform the lives of DS individuals and their communities.

Author Contribution: The entire article was conceptualized and written by the author.

Supplementary Materials: None.

Funding: None.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgements: I thank DAE for the Raja Ramanna Chair grant, the University of Mysore, and Dr Subramanya G and Chaithra S for their critical manuscript reading.

Conflicts of Interest: None..

References

1. Lana-Elola E, et al., Increased dosage of *DYRK1A* leads to congenital heart defects in a mouse model of Down syndrome. Sci Transl Med. 2024, 16(731):add6883.
2. Mégarbané A.et al., The 50th anniversary of the discovery of trisomy 21: the past, present, and future of research and treatment of Down syndrome. Genet Med. 2009, 11(9):611-616. doi: 10.1097/GIM.0b013e3181b2e34c.
3. Benhaourech S et al., Congenital heart disease and Down syndrome: various aspects of a confirmed association. Cardiovasc J Afr. 2016, 27(5):287-290. doi: 10.5830/CVJA-2016-019.
4. Lana-Elola E, et al., Genetic dissection of Down syndrome-associated congenital heart defects using a new mouse mapping panel. Elife. 2016,5:e11614.
5. Tjio JH and Levan A, The chromosome number of man, Hereditas, 1958,doi.org/10.1111/j.1601-5223.1956.tb03010.x.
6. Lejeune J, et al., Etude des chromosomes somatiques de neuf enfants mongoliens. C R Hebd Seances Acad Sci,1959,1721–1722.
7. Rahmani Z, et al. Critical role of the D21S55 region on chromosome 21 in the pathogenesis of Down syndrome. Proc Natl Acad Sci,USA ,1989,86:5958 –5962.
8. Antonarakis SE, Human chromosome 21: genome mapping and exploration, circa. Trends Genet 1993, 9(4):142-8. doi: 10.1016/0168-9525(93)90210-9.
9. Saiyed N, et al., Young mothers and higher incidence of maternal meiosis-I non- disjunction: Interplay of environmental exposure and genetic alterations during halt phase in trisomy 21, Reproductive Toxicology, 2018, 79, Pages 1-7. doi.org/10.1016/j.reprotox.2018.04.014.
10. Stoll C et al., Study of DS in 238942 consecutive births. Ann Genet, 1998, 41(1):44-51.
11. Hassold TJ and Hunt P, To err (meiotically) is human: the genesis of human aneuploidy. Nature Reviews in Genetics, 2001, 2:280-291.

12. Malini SS and Ramachandra NB, Influence of advanced age of maternal grandmothers on Down syndrome, BMC Medical Genetics, 2006, 7:4 doi:10.1186/1471-2350-7-4.

13. Gardiner K, et al., Mouse models of Down syndrome: how useful can they be? Comparison of the gene content of human chromosome 21 with orthologous mouse genomic regions. Gene. 2003; 318:137–147.

14. Smitha R, et al., Prevalence of Congenital Heart Diseases in Mysore. Indian J. Hum. Genet. 2006, 12(1):12-17.

15. Liu Y, et al., Global birth prevalence of congenital heart defects 1970-2017: Updated systematic review and meta-analysis of 260 studies. Int J Epidemiol, 2019, 48(2):455–463.

16. Katsaros, O. et al., Bicuspid Aortic Valve Disease: From Pathophysiology to Treatment. J. Clin. Med. 2024, 13, 4970.doi.org/10.3390/jcm13174970.

17. Bruneau BG, and Srivastava D. Congenital heart disease: entering a new era of human genetics. Circ Res. 2014, 14, 114(4):598-599. doi: 10.1161/CIRCRESAHA.113.303060. PMID: 24526674.

18. Parker LE and Landstrom AP, The clinical utility of pediatric cardiomyopathy genetic testing: From diagnosis to a precision medicine-based approach to care. Prog Pediatr Cardiol. 2021, 62:101413. doi: 10.1016/j.ppedcard.2021.101413. Epub doi:: 10.1016/j.ppedcard.2021.101413.

19. Courraud et al., Integrative approach to interpret DYRK1A variants, leading to a frequent neurodevelopmental disorder.Genet Med. 2021, 23(11):2150-2159. doi: 10.1038/s41436-021-01263-1.

Narrative Review

Tamarindus Indica as a potential solid polymer electrolyte material for Sodium Batteries

Kaushik P.V.N.M.*, N Krishna Jyothi, Mahantappa S Jogad, Akhilan S R, Rajesh Menon

[1]Department of Physical and Chemical Sciences, Sri Sathya Sai University for Human Excellence, Navanihal, Okali Post, Kamalapur, Kalaburagi, Karnataka - 585313

Correspondence: kaushik.p@sssuhe.ac.in

ORCID ID of corresponding author: https://orcid.org/0000-0003-4799-3479

Abstract: The role of energy storage devices in the modern-day world is phenomenal. Though lithium-ion batteries have ruled the market for several decades, few constraints have surfaced over the safety offered by them. Thus, an alternative choice of storage devices served the purpose of overcoming the setbacks of lithium batteries. The concept of polymer electrolyte is one of the greatest inventions in the field of energy storage. The invention of solid-state batteries revolutionized the battery technology over the past century. From the choice of using synthetic polymers for the preparation and fabrication of these devices, research studies have evolved to discover another class of novel materials known as 'biopolymers', which exhibit similar results as in the case of synthetic polymers, in terms of energy efficiency. Among the several reviews reported on the usage of several biopolymers in the application of energy storage devices, Tamarind Seed Polysaccharide (also known by the name *Tamarindus indica*) is one such novel biopolymer which is currently being used in the preparation of electrolyte materials for storage devices. This paper seeks to explore the similarities of biopolymers, in particular Tamarind seed polysaccharide (TSP), and discuss how its properties are similar to those exhibited by synthetic polymers, thereby concluding that bio-materials may be preferred over synthetic materials. The preference of novel biopolymers such as TSP for application in sodium batteries is discussed towards the end of this paper. The present research study seeks to establish the feasibility of application of biopolymers such as TSP in sodium-based batteries.

Keywords: Synthetic polymers, solid-state batteries, TSP, sodium batteries, biopolymers

Citation: Kaushik P. V. N. M., *et al.; Awareness* 2 (1): 30-41

Academic Editor: Dr. N. K. Lokanath

Received: Jun. 11, 2024

Revised: Nov. 26, 2024

Accepted: Nov. 28, 2024

Published: Jan. 14, 2025

1. Introduction

Since the industrial revolution, the use of energy, particularly electrical energy, has become the need of the hour. Over several decades, research studies were performed in order to make energy more accessible to all sectors of humanity.

Apart from the need for energy devices with enhanced efficiency, researchers also came up with novel ideas in order to store the produced energy and make it portable [1]. The exhausting resources of fossil fuels was never a constraint for modern man as he found suitable alternatives to replace fossil fuel resources. Among the various storage devices that were discovered and fabricated to suit the needs of modern man, batteries found their place on the top [2]. The thought that "modern day battery is a miracle" is never exaggerating, as the wide usage of batteries is seen across the spectrum, be it industry, academics, pharmacy, transport sector, etc. [3].

The evolution of batteries in the 19th century crossed various stages such as nickel cadmium battery, lead acid battery, nickel metal hydride battery etc. and finally landed at the well-known "Lithium-ion" batteries.

2. Genesis and developments in Lithium – ion batteries

Scientific studies over the past few decades lead to the conclusion that the element Lithium or Li (period 2, group 1 of the modern periodic table) exhibits several essential characteristics befitting a battery element [4]. Being a light metal with low density and lower value of standard reduction potential makes lithium a suitable material to prepare high-voltage batteries with higher densities. In the book "The Nobel Prizes 2019", Grandin [5] gives a detailed description of the latest stages in the evolution of the lithium-ion batteries (LIBs). He states that *"the discoveries of John B. Goodenough, M. Stanley Whittingham, and Akira Yoshino have arguably had a tremendous impact on our world"* (these 3 people were awarded the Nobel Prize in Chemistry 2019, for development of lithium-ion batteries).

He also states that *"Yoshino could develop an efficient, working lithium-ion battery based on the ion transfer cell configuration. The identified carbonaceous material was thus used as an anode and Goodenough's LixCoO2 material (typically containing small amounts of tin) was used as a cathode. Separator layers composed of polyethylene or polypropylene were used, and the electrolyte was composed of LiClO4 in propylene carbonate. In order to test the new configuration's safety, Yoshino devised a testing unit by which a weight could be remotely dropped on the batteries".* Further studies on LIBs also suggested the varieties of materials for electrodes and electrolytes, which enhanced the efficiency for energy storage.

However, since lithium is a reactive metal, utmost care needs to be taken to protect this metal from air and water [6]. Therefore, the careful usage of lithium was of highest importance. For example, the incident of a Boeing airline catching fire due to the explosion of a lithium battery created a necessity to enhance the safety of LIBs [7].

Also, in the work reported by Kumar et al. [8], it was stated that due to the high costs of extraction and limited availability of the lithium reserves, the application of LIBs in large-scale energy storage systems had few constraints that need to be addressed. Especially due to the unequal spread of the lithium resources and scarcity of the deposits, the future application of LIBs seems to be challenged in terms of increased costs and concerns related to environment.

3. Recent studies on solid polymer-based batteries

In order to overcome completely the safety issues of LIBs, it was necessary to replace the conventional liquid electrolytes with other suitable materials, which could be used as electrolytes, while retaining the efficiency of the output parameters [9].

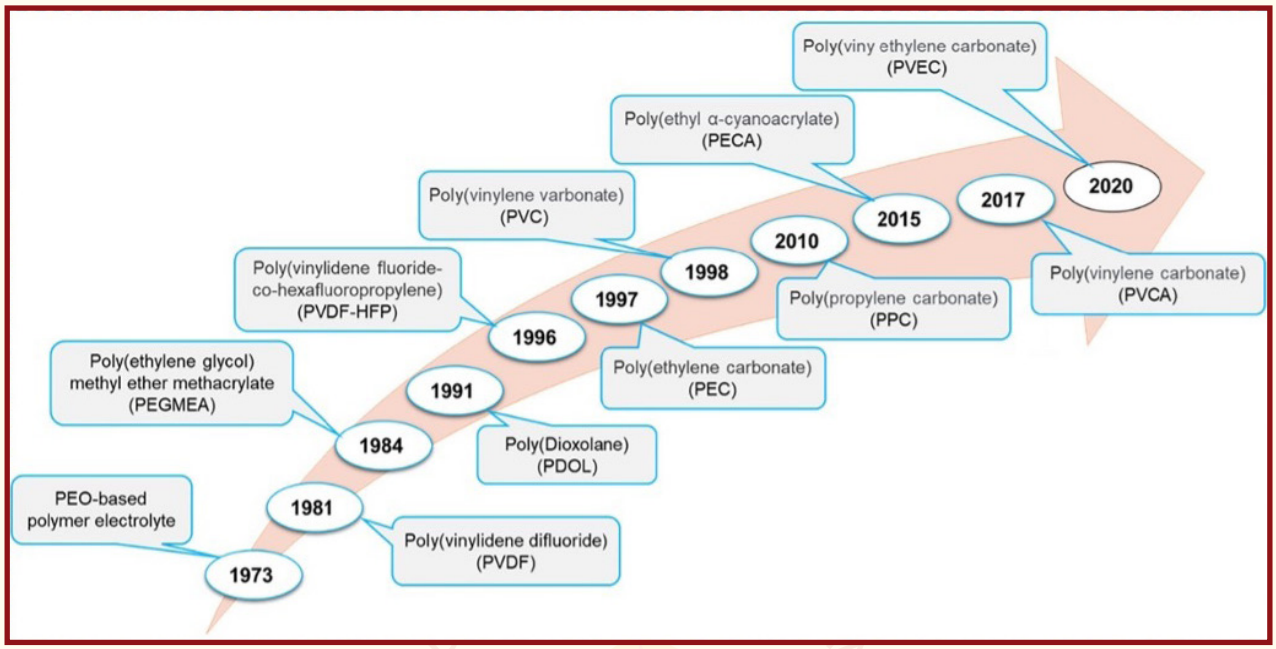


Figure 1. History of development in Polymer electrolytes (obtained from Zhang et al. [10])

In the early 70's, the concept of polymer electrolytes (PEs) created a revolution in the battery technology by improving the aspects such as safety, durability, and flexibility. Numerous research studies have been done since then in order to increase the conductivity of these PEs, through selected and suitable dopant salts and plasticizer additives. The evolution and development of polymer electrolytes is shown in figure 1.

Few main advantages of polymer electrolytes (PEs) [11] were (i) low flammability (ii) ease of processing (iii) tolerant to mechanical deformation and (iv) better electrolyte-electrode contact. In the year 2020, Hager et al. [12] reported in their work that a special type of batteries (known as polymer-based batteries) were developed using organic materials as active components in the electrodes instead of using metals and metallic compounds as redox-active materials. The stated advantages of these batteries are shown in figure 2.

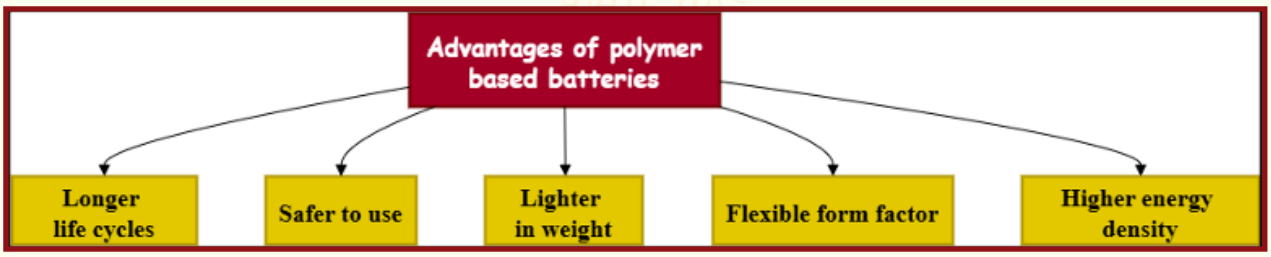


Figure 2. Advantages of polymer-based batteries

The genesis of the polymer batteries was the discovery of conducting polymers in 1970s, that led to an ever-growing demand for conducting polymers [12]. These polymer-based batteries displayed a variety of significant properties such as flexible fabrication of batteries and most importantly higher power densities. These were also found to be safe compared to LIBs [13]. However, these exhibited certain drawbacks, one being sloping of cell voltage. Eventually, the drawbacks of these were addressed through the addition of conducting additives such as carbon tubes or carbon nano fillers in order to enhance their conductivity.

Nearly 20 years after introducing the concept of PEs, researchers started to investigate and reported the preferred usage of "bio-based materials" as conventional host polymer materials, in place of synthetic polymers [14]. In their work, Rayung et al. [15] stated that *"Even though most of the polymer electrolyte theories developed to date are based on synthetic materials, they hold true for bio-based polymers as well"*.

Though synthetic polymers were preferred in replacing liquid electrolytes, the main issues to be addressed while using these are pollution and other environmental hazards, global warming, scarcity of resources, etc. These were addressed with the replacement of biopolymers as a nearly perfect renewable substitute to their counterparts.

4. Tamarind gum Biopolymer as a choice of biopolymer electrolyte

Based on the mechanism of extraction, synthesis, and origin of their source, bio-based polymers are polymers are classified into three main categories as shown in figure 3 [15].

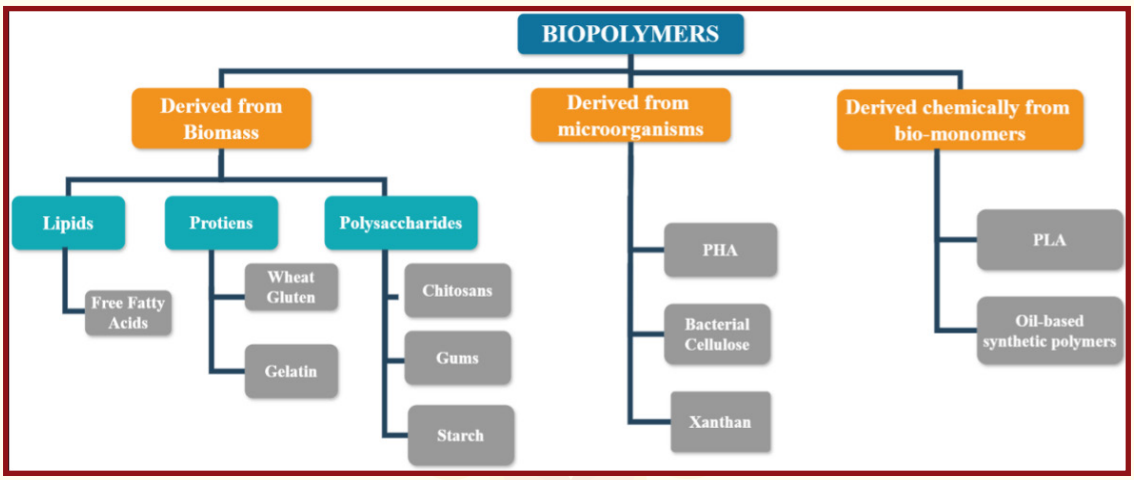


Figure 3. Classification of biopolymers

Of the several stated biopolymers that were used as polymer electrolyte materials, Tamarind gum, also known as Tamarind seed polysaccharide (TSP) is one biopolymer that has potential usage in various sectors such as food, paper industry, textile industry, jute industry, and other industries. [16–18]. The schematic structure of the Tamarind seed polysaccharide is shown in figure 4.

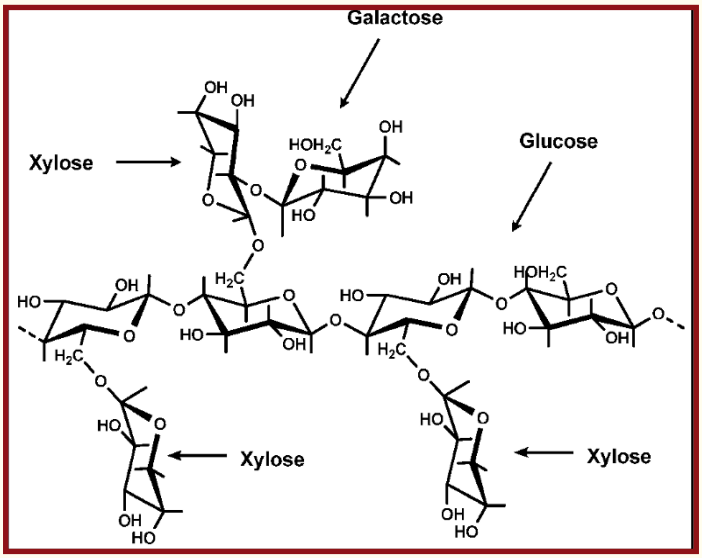


Figure 4. Schematic representation of TSP (obtained from Chawananorasest *et al.* [19])

Though several stated uses of TSP were previously listed, the application of TSP based biopolymer electrolytes was initially reported in the work of Premalatha et al. [20]. The current article lists out the results from a series of research studies done using TSP as host biopolymer and a suitable sodium salt as the dopant material, for its application in storage devices.

- In 2022, Maithilee et al. [21] reported maximum ionic conductivity value of 1.7×10^{-3} S cm^{-1} for sodium-ion conducting biopolymers prepared using TSP as the host polymer and sodium perchlorate as the dopant salt. In the same year, Premalatha et al. [22] reported maximum ionic conductivity value of 1.23×10^{-3} S cm^{-1} for proton conducting biopolymers prepared using TSP as the host polymer and ammonium formate as the dopant salt.
- In 2023, Saha et al. [23] reported maximum ionic conductivity value of 1.94×10^{-4} S cm^{-1} for biopolymers prepared using TSP as the host polymer and sodium acetate as the dopant salt.

4.1. Role of Plasticizers in improving efficiency of PEs.

In 2001, Chandrasekaran et al. [24] have reported work on PEs based on PEO and NaClO3 with PEG as the plasticizer material, Na and MnO_2 as the anode and cathode materials respectively. The results proved that addition of a suitable material (known as plasticizer) activated relaxations occurring in the polymer chain segments, that enabled ion hopping within the polymer. At room temperature, maximum conductivity of 9.47×10^{-4} S cm^{-1} was obtained.

In theory, through the addition of carbon nanotubes or fillers for a polymer will result in the formation of a network with high aspect ratio, which pave way to new pathways that are conducting, thereby enabling the overall conductivity through the reduction of interfacial resistance [25–27].

Based on similar results, research studies made through incorporation of ethylene carbonate plasticizer into the biopolymer salt complex proved an improved conductivity of the TSP biopolymer membranes. The details are given below.

- In 2023, Maithilee et al. [28] reported maximum ionic conductivity value of 1.49×10^{-3} S cm^{-1} for sodium-ion conducting biopolymers prepared using TSP as the host polymer and sodium nitrite as dopant salt.

The summary of TSP based biopolymer electrolytes prepared using sodium as the dopant salt is tabulated below.

Table 1. Review on sodium salt doped TSP based biopolymer electrolytes for storage devices

Sl. No	Sodium Dopant salt used	Highest conducting composition	Reported Conductivity (in S cm^{-1}) exhibited by the highest conducting film	Date of Publishing
1	Sodium perchlorate ($NaClO_4$)	1 g TSP + 0.8 g $NaClO_4$	1.70×10^{-3}	Jan-22
2	Sodium nitrite ($NaNO_2$) + Ethylene Carbonate (EC) plasticizer	1 g TSP + 0.7 wt.% $NaNO_2$ + 0.5 wt.% EC	1.49×10^{-3}	Jun-23
3	Sodium acetate (CH_3COONa)	(TSP: CH_3COONa) = 80:20 wt.%	1.95×10^{-4}	Sep-23

From the above examples, it was seen that when sodium salts were doped to TSP, conductivities of the order of 10^{-4} S cm^{-1} and 10^{-3} S cm^{-1} were obtained. Thrisha et al. [29] stated that the size and ion mobility play a very crucial role in the ionic conductivity of PEs. Salt doped PEs with ions of smaller sizes (like Na^+ ions) exhibited greater conductivity. In the same work, it was stated that the interaction between the dopant salt and the host polymer can give rise to several amorphous regions, thereby reducing the crystallinity and increasing the conductivity. It was reported in their study that certain salts had the property of forming stable complexes while maintaining constant conductivity over time and others have not shown such property. Along with the choice of the dopant salts, the addition of suitable plasticizers and ionic liquids will further enhance the conductivity achieved [30].

In the preparation of polymer electrolytes, Rayung et al. [15] state that *"for the construction of polymer electrolytes, several factors should be taken into consideration, including the choice of polymer host, the salts/acid dopants. The polymer host should possess certain characteristics such as good chemical, electrochemical, and photochemical stability, as well as good thermal and mechanical properties. Further, host polymers with a high concentration of polar groups (containing electron donors: O, NH, CN, F) are preferred. It is important to develop host polymers which have few crystalline phases and a relatively low glass transition temperature."*

5. Sodium as a substitute for Li batteries

The properties such as chemical, electrochemical and photochemical properties of synthetic polymers is well established in the research studies of several scientists [31–35]. However, for biopolymers such as TSP, recent research studies reported that they also exhibited good properties, as stated above. Sampathkumar et al. [36] have reported in their work that the property of electrochemical stability exhibited by TSP, to withstand fluctuations in the voltage and exhibit structural steadiness during the charge-discharge cycle, is one of the key factors in deciding the usage of TSP biopolymer electrolytes in batteries and supercapacitors. In terms of chemical stability, Monisha et al. [37] found that due to the nature of the origin and due to the power of resistance to decay in variety of environments exhibited by TSP, the electrochemical stability exhibited by TSP is in good comparison to synthetic polymers. Since TSP is not susceptible to chemical reactions, it is better suited for those applications where mild exposure of the material to reactive compounds such as acids or bases is expected. With respect to the property of photochemical stability, Malvia et al. [38] have reported that a substance is prone to photodegradation, when it contains a group of molecules called 'chromophores'. This is also reported in the work of Dluga et al. [39]. From the work of Malvia et al., it is an indicative factor that TSP might show good photochemical stability. Thus, for optimum performance of a solid-state battery, the choice of biopolymers (like TSP) over synthetic polymers may be proposed and accepted.

The available choice of Sodium-ion batteries in comparison to Lithium-ion batteries are stated henceforth. An interesting fact from the 1870 novel "Twenty Thousand Leagues Under the Sea" by Jules Verne describes the submarine *Nautilus* powered by an advanced battery assembly unit. In the course of the novel, Captain Nemo mentions [40] that *"…the cells with sodium must be regarded as most energetic, and that their electromotive force is double that of the zinc cells."* Though this was just mentioned on a casual note in the novel, the very first prototype of a sodium metal based solid-state battery was reported by Kumar et al. [8] which was fabricated and assembled by M. Armand, using the sodium metal as negative electrode, β-alumina as the solid electrolyte, and chromium oxide/ graphite intercalation compound (CrO_3 @graphite) at the positive electrode in the year 1972. The use of preferring sodium as a substitute for lithium can be well understood through a careful observation of figure 5.

	Sodium batteries	Lithium batteries
Energy density	≈ 150	≈ 250
Cyclability	≈ 4000	≈ 2000
Voltage	≈ 3.7	≈ 4
Efficiency	Lower	Higher
Safety	High	Medium
Need for critical raw materials	No	Yes
Cost	Less costly and less volatile	More expensive and more volatile
Size	Bulky	Light
Low temperature performance	Good performance	Lower performance
Charging and discharging time	Fast in both cases. Allows 100 % discharge	Longer duration
Flammability	Non-flammable	Flammable
Recyclability	Moderate	Difficult

The options highlighted with a lightning bolt are the most advantageous for each characteristic.

Figure 5. Differences between Li-ion and Na-ion batteries
(Source: https://www.iberdrola.com/documents/20125/3225538/baterias-iones-sodio-infografia-EN.pdf)

Compared to the extensively-used lithium-ion (Li-ion) batteries, Na-ion batteries have a lower energy density and cycle life, but they perform better in a wide operational temperature range and are safer. Na-ion cells have a similar working principle to Li-ion cells and are expected to be at least 20% cheaper than LFP due to their lithium-free nature [41,42]. However, separator and electrolyte costs could be significant and result in Na-ion being more costly. Figure 6 shows the comparison between Li-ion and Na-ion batteries.

A sodium battery is basically a battery that deploys Na+ ions as the charge carriers. The working principle of this battery is similar to that of LIB except the fact that lithium ions are replaced by sodium ions [43].

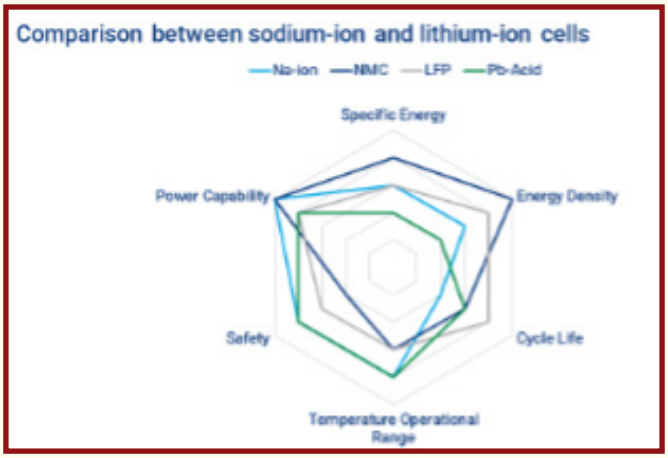


Figure 6. Comparison between Li-ion and Na-ion batteries
(Source: Wood Mackenzie https://www.woodmac.com/news/opinion/will-sodium-ion-battery-cells-be-a-game-changer-for-electric-vehicle-and-energy-storage-markets)

Current studies are addressing the minor drawbacks of sodium ion batteries, one such being lower energy density [44,45]. However, the choice of sodium comes from the fact that elements belonging to the same group exhibit similar chemical properties. The added advantages of these over lithium batteries paved way to the commercialization of sodium batteries.

6. Conclusion

In the recent work of Kumar et al. [8], the best suited polymers for Na-ion batteries are depicted in Figure 7.

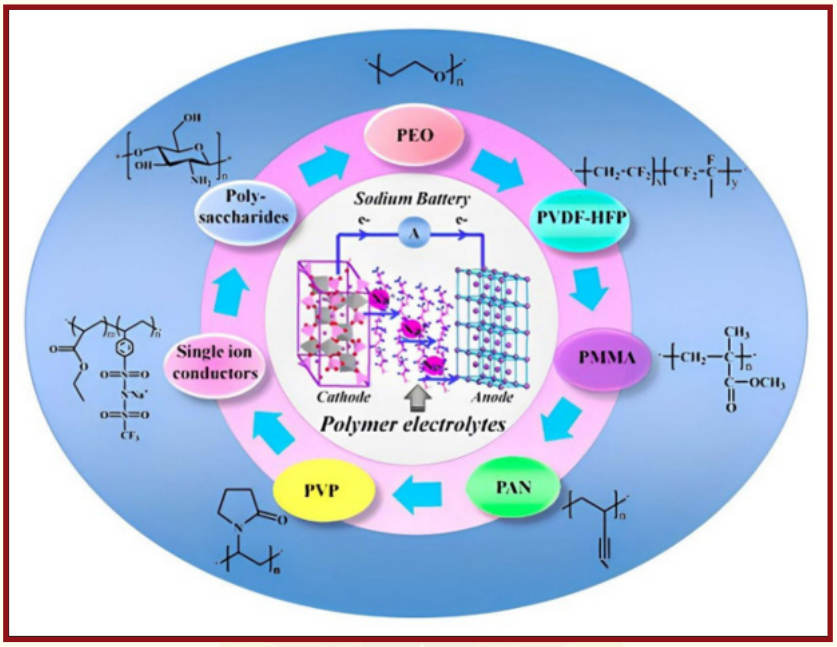


Figure 7. Polymer Electrolytes for Sodium batteries (obtained from Kumar et al. [8])
Copyright 2019, American Chemical Society

Although there are certain limitations of biopolymers, such as relatively weaker mechanical strengths [46] and challenges in processing [47], there are potential advantages these offer, such as biocompatibility, sustainability, biodegradable nature and ecological nature. Therefore, these are preferred in comparison to synthetic polymers [48–50]. Thus, for the fabrication of a solid-state battery, the preference of using TSP biopolymer as a substitute to the conventional synthetic polymers is preferred [51,52]. Apart from this, the preference of sodium metal in place of lithium metal, from a perspective that in the coming times, biopolymer-based sodium batteries will rule the future of modern-day solid-state battery technology. Though extensive ongoing research is focused on in the applications of Na-ion batteries in place of lithium batteries, the choice of preferring sodium ion batteries is mainly due to their cost-effectiveness, recyclability, and better performance even at lower temperatures as compared to lithium batteries [53]. Resolving the issues like the energy density of sodium batteries and enhancement of the conductivity of biopolymer electrolytes will definitely be considered as suitable solutions for large scale production of these batteries with minimum cost [54]..

Author Contributions: Conceptualization - P.V.N.M and N.K.J; Methodology - M.S.J; writing—original draft preparation – P.V.N.M, A.S.R and R.M; writing—review and editing – P.V.N.M, N.K.J and M.S.J;

Funding: This research received no external funding.

Acknowledgments: The authors are grateful to the University for enabling them to pursue research in this field.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. A. Riaz, M.R. Sarker, M.H.M. Saad, R. Mohamed, Review on Comparison of Different Energy Storage Technologies Used in Micro-Energy Harvesting, WSNs, Low-Cost Microelectronic Devices: Challenges and Recommendations, Sensors 21 (2021) 5041. https://doi.org/10.3390/s21155041.
2. E. Hossain, H. Faruque, Md. Sunny, N. Mohammad, N. Nawar, A Comprehensive Review on Energy Storage Systems: Types, Comparison, Current Scenario, Applications, Barriers, and Potential Solutions, Policies, and Future Prospects, Energies 13 (2020) 3651. https://doi.org/10.3390/en13143651.
3. H.B. Glushakow, In Search of an Energy Miracle, in: 2021 4th International Conference on Energy Conservation and Efficiency (ICECE), IEEE, Lahore, Pakistan, 2021: pp. 1–6. https://doi.org/10.1109/ICECE51984.2021.9406305.
4. E.G. Garrison, A history of engineering and technology: artful methods, 2nd ed, CRC Press, Boca Raton, Fla, 1999.
5. K. Grandin, The Nobel Prizes 2019, WORLD SCIENTIFIC, 2022. https://doi.org/10.1142/12826.
6. N. Bolan, S.A. Hoang, M. Tanveer, L. Wang, S. Bolan, P. Sooriyakumar, B. Robinson, H. Wijesekara, M. Wijesooriya, S. Keerthanan, M. Vithanage, B. Markert, S. Fränzle, S. Wünschmann, B. Sarkar, A. Vinu, M.B. Kirkham, K.H.M. Siddique, J. Rinklebe, From mine to mind and mobiles – Lithium contamination and its risk management, Environmental Pollution 290 (2021) 118067. https://doi.org/10.1016/j.envpol.2021.118067.
7. N. Williard, W. He, C. Hendricks, M. Pecht, Lessons Learned from the 787 Dreamliner Issue on Lithium-Ion Battery Reliability, Energies 6 (2013) 4682–4695. https://doi.org/10.3390/en6094682.
8. S. Kumar, R. Raghupathy, M. Vittadello, Sodium Polymer Electrolytes: A Review, Batteries 10 (2024) 73. https://doi.org/10.3390/batteries10030073.
9. M. Pigłowska, B. Kurc, M. Galiński, P. Fuć, M. Kamińska, N. Szymlet, P. Daszkiewicz, Challenges for Safe Electrolytes Applied in Lithium-Ion Cells—A Review, Materials 14 (2021) 6783. https://doi.org/10.3390/ma14226783.
10. D. Zhang, S. Li, Q. Xiong, Z. Huang, H. Hong, S. Yang, J. Zhu, C. Zhi, Interface challenges and research progress toward solid polymer electrolytes-based lithium metal batteries, MetalMat 1 (2024) e13. https://doi.org/10.1002/metm.13.
11. Y. An, X. Han, Y. Liu, A. Azhar, J. Na, A.K. Nanjundan, S. Wang, J. Yu, Y. Yamauchi, Progress in Solid Polymer Electrolytes for Lithium-Ion Batteries and Beyond, Small 18 (2022) 2103617. https://doi.org/10.1002/smll.202103617.
12. M.D. Hager, B. Esser, X. Feng, W. Schuhmann, P. Theato, U.S. Schubert, Polymer-Based Batteries—Flexible and Thin Energy Storage Systems, Advanced Materials 32 (2020) 2000587. https://doi.org/10.1002/adma.202000587.
13. J. Kalhoff, G.G. Eshetu, D. Bresser, S. Passerini, Safer Electrolytes for Lithium-Ion Batteries: State of the Art and Perspectives, ChemSusChem 8 (2015) 2154–2175. https://doi.org/10.1002/cssc.201500284.
14. A. Kumar, G. Sharma, Mu. Naushad, A.H. Al-Muhtaseb, A. García-Peñas, G.T. Mola, C. Si, F.J. Stadler, Bio-inspired and biomaterials-based hybrid photocatalysts for environmental detoxification: A review, Chemical Engineering Journal 382 (2020) 122937. https://doi.org/10.1016/j.cej.2019.122937.
15. M. Rayung, M.M. Aung, S.C. Azhar, L.C. Abdullah, M.S. Su'ait, A. Ahmad, S.N.A.M. Jamil, Bio-Based Polymer Electrolytes for Electrochemical Devices: Insight into the Ionic Conductivity Performance, Materials 13 (2020) 838. https://doi.org/10.3390/ma13040838.
16. B.B. Mansingh, J.S. Binoj, N.P. Sai, S.A. Hassan, S. Siengchin, M.R. Sanjay, Y.C. Liu, Sustainable development in utilization of Tamarindus indica L. and its by-products in industries: A review, Current Research in Green and Sustainable Chemistry 4 (2021) 100207. https://doi.org/10.1016/j.crgsc.2021.100207.

17. C.K. Nagar, S.K. Dash, K. Rayaguru, Tamarind seed: Composition, applications, and value addition: A comprehensive review, Food Processing Preservation 46 (2022). https://doi.org/10.1111/jfpp.16872.

18. H. Zhang, H. Cui, F. Xie, Z. Song, L. Ai, Tamarind seeds polysaccharide: Structure, properties, health benefits, modification and food applications, Food Hydrocolloids (2024) 110222. https://doi.org/10.1016/j.foodhyd.2024.110222.

19. K. Chawananorasest, P. Saengtongdee, P. Kaemchantuek, Extraction and Characterization of Tamarind (Tamarind indica L.) Seed Polysaccharides (TSP) from Three Difference Sources, Molecules 21 (2016) 775. https://doi.org/10.3390/molecules21060775.

20. M. Premalatha, T. Mathavan, S. Selvasekarapandian, S. Monisha, D.V. Pandi, S. Selvalakshmi, Investigations on proton conducting biopolymer membranes based on tamarind seed polysaccharide incorporated with ammonium thiocyanate, Journal of Non-Crystalline Solids 453 (2016) 131–140. https://doi.org/10.1016/j.jnoncrysol.2016.10.008.

21. K. Maithilee, P. Sathya, S. Selvasekarapandian, R. Chitra, M.V. Krishna, S. Meyvel, Na-ion conducting biopolymer electrolyte based on tamarind seed polysaccharide incorporated with sodium perchlorate for primary sodium-ion batteries, Ionics 28 (2022) 1783–1790. https://doi.org/10.1007/s11581-022-04440-7.

22. M. Premalatha, S. Monisha, S. Selvalakshmi, T. Mathavan, V. Moniha, Investigation of hydrogen ion transport in NH4HCO2 doped TSP biopolymer electrolyte for battery applications, Materials Letters 320 (2022) 132369. https://doi.org/10.1016/j.matlet.2022.132369.

23. A. Saha, K.V. Kumar, N.K. Jyothi, M.G. Kiran, M.C. Rao, Structural and electrical properties of TSP: CH3COONa amorphous Biopolymer electrolytes for electrochemical cell applications, Journal of Non-Crystalline Solids 616 (2023) 122465. https://doi.org/10.1016/j.jnoncrysol.2023.122465.

24. R. Chandrasekaran, S. Selladurai, Preparation and characterization of a new polymer electrolyte (PEO:NaClO3) for battery application, J Solid State Electrochem 5 (2001) 355–361. https://doi.org/10.1007/s1000800000156.

25. Y. Gao, F. Qu, W. Wang, F. Li, X. Zhao, L. Zhang, Increasing the electrical conductivity of polymer nanocomposites under the external field by tuning nanofiller shape, Composites Science and Technology 176 (2019) 37–45. https://doi.org/10.1016/j.compscitech.2019.03.025.

26. M. Ikram, A. Raza, A. Shahbaz, H. Ijaz, S. Ali, A. Haider, M. Tayyab Hussain, J. Haider, A. Ahmed Rafi, S. Ali, Carbon Nanotubes, in: M. Ikram, A. Maqsood (Eds.), 21st Century Advanced Carbon Materials for Engineering Applications - A Comprehensive Handbook, IntechOpen, 2021. https://doi.org/10.5772/intechopen.95442.

27. A. Chanda, S.K. Sinha, N.V. Datla, Electrical conductivity of random and aligned nanocomposites: Theoretical models and experimental validation, Composites Part A: Applied Science and Manufacturing 149 (2021) 106543. https://doi.org/10.1016/j.compositesa.2021.106543.

28. K. Maithilee, P. Sathya, S. Selvasekarapandian, R. Chitra, S. Meyvel, Investigation on tamarind seed polysaccharide biopolymer electrolyte doped with sodium nitrite and EC plasticizer for primary sodium battery, Bull Mater Sci 46 (2023) 114. https://doi.org/10.1007/s12034-023-02948-w.

29. Thrisha K, Saratha R, Natural polymer-based electrolytes for energy storage devices—an overview, Ionics 30 (2024) 1245–1266. https://doi.org/10.1007/s11581-023-05315-1.

30. F.C. Tavares, C.M. Cholant, E.C. Kohlrausch, G. R. Bolzan, P.F.B. Gonçalves, E.S. Gil, S. Khan, J. Dupont, C.O. Avellaneda, M.J. Leite Santos, Ionic Liquid Boosted Conductivity of Biopolymer Gel Electrolyte, J. Electrochem. Soc. 170 (2023) 084501. https://doi.org/10.1149/1945-7111/ace937.

31. T. Celiker, R. İsci, K. Kaya, T. Ozturk, Y. Yagci, Photoinduced STEP-GROWTH polymerization of thieno[3,4-b] thiophene derivatives. The substitution effect on the reactivity and electrochemical properties, Journal of Polymer Science 58 (2020) 2327–2334. https://doi.org/10.1002/pol.20200398.

32. J. Liu, L. Lu, D. Wood, S. Lin, New Redox Strategies in Organic Synthesis by Means of Electrochemistry and Photochemistry, ACS Cent. Sci. 6 (2020) 1317–1340. https://doi.org/10.1021/acscentsci.0c00549.

33. D. Hao, Y. Liu, S. Gao, H. Arandiyan, X. Bai, Q. Kong, W. Wei, P.K. Shen, B.-J. Ni, Emerging artificial nitrogen cycle processes through novel electrochemical and photochemical synthesis, Materials Today 46 (2021) 212–233. https://doi.org/10.1016/j.mattod.2021.01.029.

34. G. Singh, S. Chandra, Unravelling the structural-property relations of porphyrinoids with respect to photo- and electro-chemical activities, Electrochemical Science Adv 3 (2023) e2100149. https://doi.org/10.1002/elsa.202100149.

35. N. Singh, U. Riaz, Recent trends on synthetic approaches and application studies of conducting polymers and copolymers: a review, Polym. Bull. 79 (2022) 10377–10408. https://doi.org/10.1007/s00289-021-03987-1.

36. L. Sampathkumar, P. Christopher Selvin, S. Selvasekarapandian, P. Perumal, R. Chitra, M. Muthukrishnan, Synthesis and characterization of biopolymer electrolyte based on tamarind seed polysaccharide, lithium perchlorate and ethylene carbonate for electrochemical applications, Ionics 25 (2019) 1067–1082. https://doi.org/10.1007/s11581-019-02857-1.

37. S. Monisha, P. Prameela, G. Boopathi, S. Selvalakshmi, S. Gnanam, J. Gajendiran, Synthesis, structural properties, thermal behavior, and electrical and electrochemical sensing performance of tamarind seed polysaccharide-lithium nitrate polymer electrolyte, Ionics 30 (2024) 2807–2818. https://doi.org/10.1007/s11581-024-05439-y.

38. R. Malviya, S. Sundram, S. Fuloria, V. Subramaniyan, K.V. Sathasivam, A.K. Azad, M. Sekar, D.H. Kumar, S. Chakravarthi, O. Porwal, D.U. Meenakshi, N.K. Fuloria, Evaluation and Characterization of Tamarind Gum Polysaccharide: The Biopolymer, Polymers 13 (2021) 3023. https://doi.org/10.3390/polym13183023.

39. A. Długa, D. Bajer, H. Kaczmarek, Photochemical and Thermal Stability of Bionanocellulose/Poly(Vinyl Alcohol) Blends, Polymers 14 (2022) 4364. https://doi.org/10.3390/polym14204364.

40. Z. Song, F. Chen, M. Martinez-Ibañez, W. Feng, M. Forsyth, Z. Zhou, M. Armand, H. Zhang, A reflection on polymer electrolytes for solid-state lithium metal batteries, Nat Commun 14 (2023) 4884. https://doi.org/10.1038/s41467-023-40609-y.

41. M. Li, H. Zhuo, Q. Jing, Y. Gu, Z. Liao, K. Wang, J. Hu, D. Geng, X. Sun, B. Xiao, Low-temperature performance of Na-ion batteries, Carbon Energy 6 (2024) e546. https://doi.org/10.1002/cey2.546.

42. S.S.A. Kumar, M. Nujud Badawi, J. Liew, T. Prasankumar, K. Ramesh, S. Ramesh, S. Ramesh, S.K. Tiong, High-Performance Sodium-Ion Batteries with Graphene: An Overview of Recent Developments and Design, ChemSusChem (2024) e202400958. https://doi.org/10.1002/cssc.202400958.

43. N. Tapia-Ruiz, A.R. Armstrong, H. Alptekin, M.A. Amores, H. Au, J. Barker, R. Boston, W.R. Brant, J.M. Brittain, Y. Chen, M. Chhowalla, Y.-S. Choi, S.I.R. Costa, M. Crespo Ribadeneyra, S.A. Cussen, E.J. Cussen, W.I.F. David, A.V. Desai, S.A.M. Dickson, E.I. Eweka, J.D. Forero-Saboya, C.P. Grey, J.M. Griffin, P. Gross, X. Hua, J.T.S. Irvine, P. Johansson, M.O. Jones, M. Karlsmo, E. Kendrick, E. Kim, O.V. Kolosov, Z. Li, S.F.L. Mertens, R. Mogensen, L. Monconduit, R.E. Morris, A.J. Naylor, S. Nikman, C.A. O'Keefe, D.M.C. Ould, R.G. Palgrave, P. Poizot, A. Ponrouch, S. Renault, E.M. Reynolds, A. Rudola, R. Sayers, D.O. Scanlon, S. Sen, V.R. Seymour, B. Silván, M.T. Sougrati, L. Stievano, G.S. Stone, C.I. Thomas, M.-M. Titirici, J. Tong, T.J. Wood, D.S. Wright, R. Younesi, 2021 roadmap for sodium-ion batteries, J. Phys. Energy 3 (2021) 031503. https://doi.org/10.1088/2515-7655/ac01ef.

44. K. Mathiyalagan, D. Shin, Y.-C. Lee, Difficulties, strategies, and recent research and development of layered sodium transition metal oxide cathode materials for high-energy sodium-ion batteries, Journal of Energy Chemistry 90 (2024) 40–57. https://doi.org/10.1016/j.jechem.2023.10.023.

45. J. Chen, G. Adit, L. Li, Y. Zhang, D.H.C. Chua, P.S. Lee, Optimization Strategies Toward Functional Sodium-Ion Batteries, Energy & Environ Materials 6 (2023) e12633. https://doi.org/10.1002/eem2.12633.

46. K.M. Zia, N. Akram, S. Tabasum, A. Noreen, M.U. Akbar, Processing of bio-based polymers, in: Processing Technology for Bio-Based Polymers, Elsevier, 2021: pp. 151–189. https://doi.org/10.1016/B978-0-323-85772-7.00003-3.

47. T. Gurunathan, S. Mohanty, S.K. Nayak, A review of the recent developments in biocomposites based on natural fibres and their application perspectives, Composites Part A: Applied Science and Manufacturing 77 (2015) 1–25. https://doi.org/10.1016/j.compositesa.2015.06.007.

48. L. Manfra, V. Marengo, G. Libralato, M. Costantini, F. De Falco, M. Cocca, Biodegradable polymers: A real opportunity to solve marine plastic pollution?, Journal of Hazardous Materials 416 (2021) 125763. https://doi.org/10.1016/j.jhazmat.2021.125763.

49. S. Walker, R. Rothman, Life cycle assessment of bio-based and fossil-based plastic: A review, Journal of Cleaner Production 261 (2020) 121158. https://doi.org/10.1016/j.jclepro.2020.121158.

50. G. Satchanska, S. Davidova, P.D. Petrov, Natural and Synthetic Polymers for Biomedical and Environmental Applications, Polymers 16 (2024) 1159. https://doi.org/10.3390/polym16081159.

51. J. Ding, Y. Yang, J. Poisson, Y. He, H. Zhang, Y. Zhang, Y. Bao, S. Chen, Y.M. Chen, K. Zhang, Recent Advances in Biopolymer-Based Hydrogel Electrolytes for Flexible Supercapacitors, ACS Energy Lett. 9 (2024) 1803–1825. https://doi.org/10.1021/acsenergylett.3c02567.

52. N. Borah, A. Kar, N. Karak, Biocomposites of biopolymers with metals and their derivatives, in: Advances in Biocomposites and Their Applications, Elsevier, 2024: pp. 167–200. https://doi.org/10.1016/B978-0-443-19074-2.00006-X.

53. C. Vaalma, D. Buchholz, M. Weil, S. Passerini, A cost and resource analysis of sodium-ion batteries, Nat Rev Mater 3 (2018) 18013. https://doi.org/10.1038/natrevmats.2018.13.

54. W. Zhao, M. Wang, H. Lin, K. Kim, R. He, S. Feng, H. Liu, Research progress on electrolyte key salts for sodium-ion batteries, Progress in Natural Science: Materials International 34 (2024) 263–273. https://doi.org/10.1016/j.pnsc.2024.03.003.


SRI SATHYA SAI UNIVERSITY FOR HUMAN EXCELLENCE
योगः कर्मसु कौशलम्