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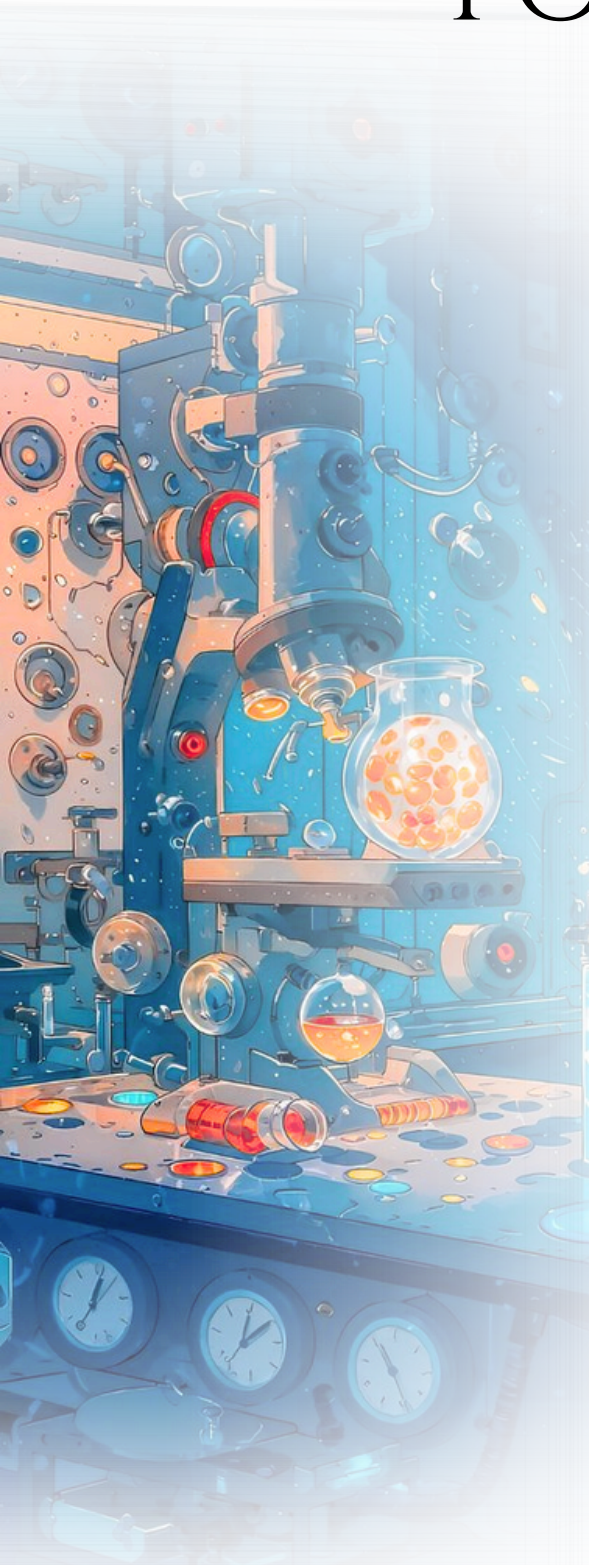
FOREWORD



Science has always been a mirror of the future, the past and the present. Thanks to science, we interpret reality and set sail toward new perspectives. Also, science is an instrument that helps us push beyond the limits that were previously thought insuperable. Our mission is to bring this instrument to everyone and to overcome those limits.

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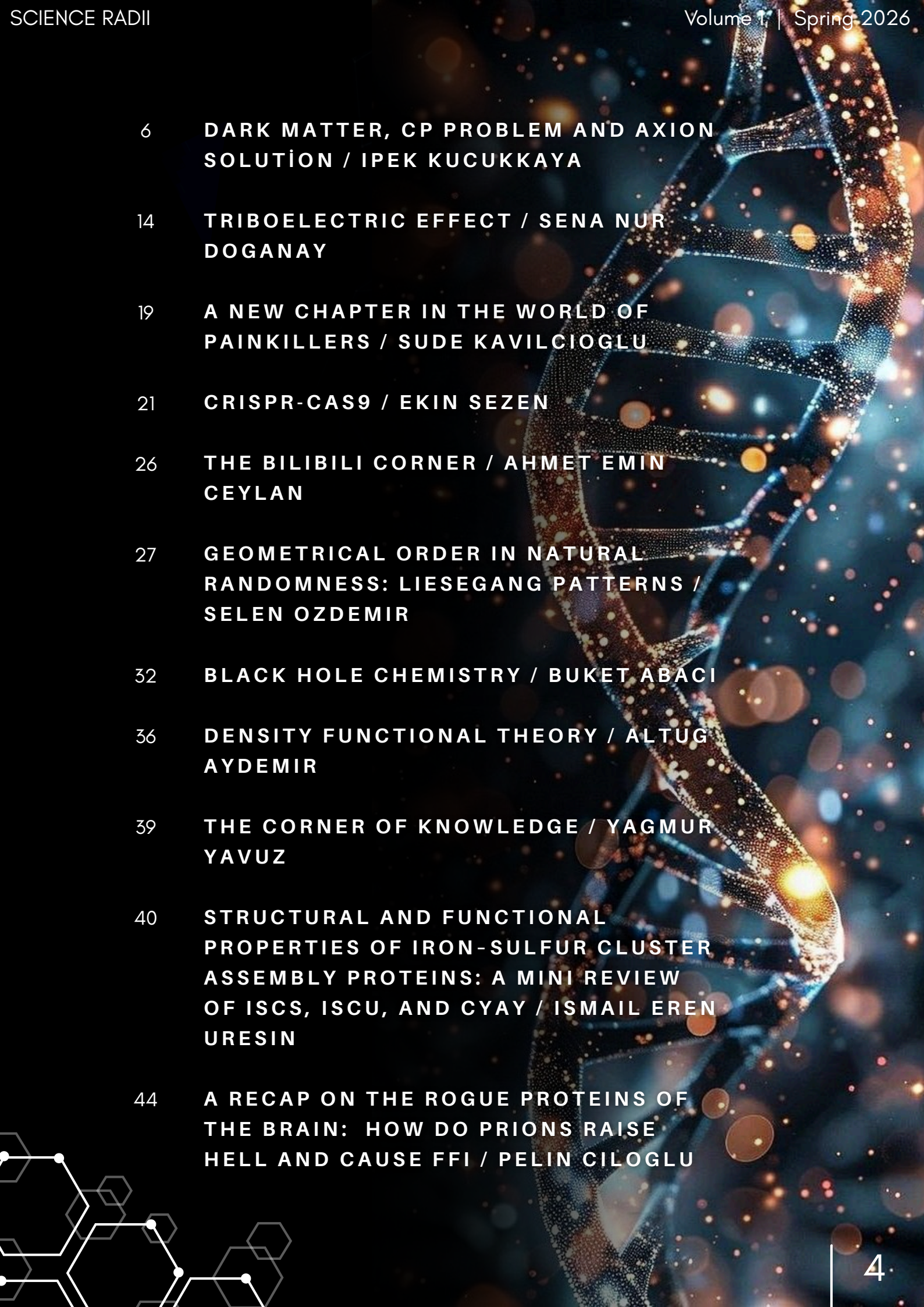
The Science Literacy Society was founded to share this priceless process with the people who want to see the beyond and to invite them into this adventure. As members of this society, we would like to share what we learn and what we think with those people and create a scientific atmosphere that every individual from different background can understand.

Science Radii is a science magazine that brings together articles from every corner of science, and our purpose is to offer you, our valued readers, fresh and interesting perspectives on different aspects of life.

Batuhan Usta
Founder of Science Literacy Society

TABLE OF CONTENTS



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Dark Matter, CP Problem and Axion Solution

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This article investigates how cosmology, particle physics, and electromagnetism intersect at an essential proposition to dark matter: a particle called the ”Axion”. An axion is described by significant mathematical viewpoints using Quantum Field Theory. Axion is akin to an overture to a new paradigm in physics; it is a solution to a symmetry problem in the physics of the strong interaction that occurs inside the atomic nucleus. It will be described using certain symmetries and fundamental concepts in electromagnetism, such as dipoles. Furthermore, axion's early universe appearance scenarios will also be addressed.

Introduction

The Axion idea emerged nearly in the 1980s because of the thought that it could be a candidate for dark matter. It is related to Quantum Chromodynamics (QCD), which is a type of quantum field theory that explains the strong interactions between quarks and gluons. Charge Parity (CP) symmetry is the conserved symmetry of the system when charge conjugation (C) and parity transformations (P) are applied, which will be further explained in the ”Symmetries” subsection.

In QCD, it is observed that this symmetry is never violated and the proposition to why it is never violated is the axion. This proposition is also a candidate for dark matter. Dark matter is a form of matter that is not able to generate light, but it can be detected gravitationally. One of the propositions is that it may ”populate the universe in a wave-like state,” which is cold and moving very slowly. Axion complies with this wave-like property since its field is described as oscillatory. Hence, it is one of the major reasons it is a candidate for dark matter [1].

What is Dark Matter

Dark matter is one of the most prominent topics in both cosmology and particle physics. It is known that the total mass of dark matter and visible (normal) matter comprises 32% of the universe, 26% dark matter, and 6% visible matter. The remaining 68% is composed of dark energy [1]. Dark matter is different from visible matter. Visible matter shapes stars and generates light that can be detected through telescopes. Dark matter is a matter that has mass, but it neither directly forms big clusters and formations like visible matter nor interacts with electromagnetic waves.

This is because its interaction with visible matter is only through gravity. It has a major role in the formation of galaxies. Dark matter haloes (spherical regions) are formed by the gravitational collapse of small cosmological structures. This occurs hierarchically, meaning that this repeats over time to form bigger structures. Consequently, galaxies form at the center of dark matter haloes. In the following figure (Fig. 1), this phenomenon is shown by color density. The darker (green) regions of the color show that there are galaxy formations, whereas the lighter (yellow) regions correspond to the early stage: dark matter haloes before galaxy formations [2].

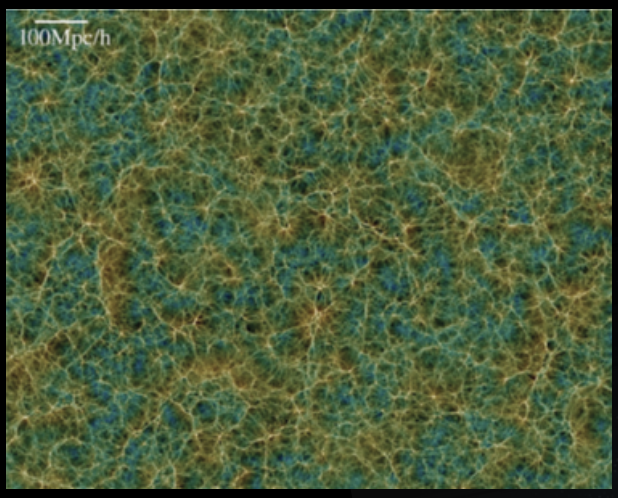

Fig 1. Distribution of dark matter over cosmological scales in the field of galaxy formation [3]

Expansion of the Universe

Dark matter and dark energy are dissimilar concepts, even though they may look similar. Dark energy is the primary reason why the universe continues to expand. Einstein demonstrated that the rate of expansion of the universe is determined by the energy density and total matter, and he postulated that as the universe expands, the total matter density (comprising both dark and visible matter) decreases. The reason is that the volume increases, but the total matter density is the same everywhere. However, the dark energy density should remain constant because, as the volume increases, dark energy will still be present in the same proportion in the new volume, as it plays the role of a cosmological constant. Therefore, the dark energy fraction increases when compared to the total matter density, and the universe will expand, and the rate of expansion will increase. Dark matter slows down the expansion rate by its mass and gravity. So it does not cause a positive acceleration in the expansion of the universe [4].

Expectations and Observations

There have been some experiments conducted on the existence of dark matter. One of these experiments was in 1959. Louise Volders had measured the velocity of hydrogen gas in the galaxy ”Triangulum”, using hydrogen’s atomic transitions and the ”redshift” phenomenon, which is described as a decrease in frequency. According to Newton’s second law, orbit velocity is proportional to the square root of the total mass; the total amount of matter inside the orbit of the hydrogen gas. He found that the velocity of the hydrogen gas was higher than expected, because the total mass of the stars inside the orbit in Triangulum is not able to provide that high speed value. Therefore, it was concluded that there should be more mass than the total mass of the stars, which is dark matter. In Fig. 2, when a graph of velocity versus distance from the center of the galaxy is plotted, the dotted line describes the expected graph and the solid line describes the measured values plotted on the graph [4]. In the following subsections, a candidate for dark matter,” axion,” will be presented. Before, some fundamental concepts will be introduced.

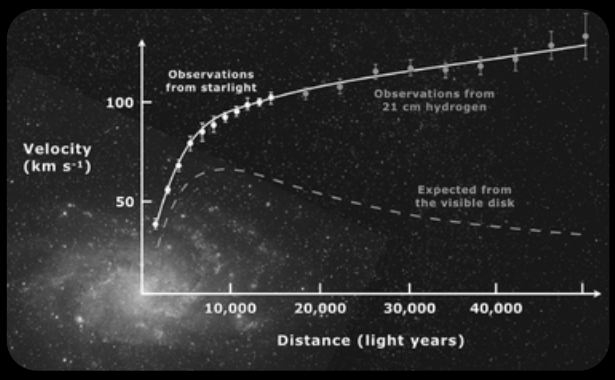

Fig 2. Rotation curve of Triangulum [4]

FUNDAMENTAL CONCEPTS

Transformations

In nature, there are some transformations that do not violate the laws of physics. These transformations are: time transformation, parity transformation, and charge conjugation. Time transformation involves reversing the flow of time (i.e., a video of a pendulum swinging back). Parity transformation reverses the spatial coordinates. It is similar to taking mirror symmetry. For instance, the (x,y,z) coordinate becomes (-x,-y,-z). Charge conjugation is the transformation of a particle into its antiparticle by reversing all of its charges [5]. There are many examples to this phenomenon: The electrical charge +e ($1.602176634 \times 10^{-19}$ C) [6] becomes -e, the proton becomes an antiproton, the electron e^- becomes positron e^+, and so on.

Symmetries

There are some symmetries that emerge due to these physical transformations. One of them is the charge parity (CP) symmetry. In this symmetry, every particle is replaced with its antiparticle, and a mirror reflection is applied to its spatial coordinates. Another symmetry is the charge parity-time reversal symmetry (CPT). This symmetry includes the time reversal transformation in addition to the properties of CP. Also, it has never been observed to be violated in experiments [1].

Lagrangian

Lagrangian is described as the fact that a physical path will be chosen in order to minimize the time integral of the difference between the kinetic and potential energies.
It is given by the equation:

$$L = T - U \quad (1)$$

where **L** is the Lagrangian, T is the kinetic energy, and U is the potential energy. The intuitive approach to taking this integral is that the kinetic energy will determine the speed of the movement of the system, whereas the potential energy will determine the accumulated energy in the system. Taking their difference will connect these two energies to each other in an equation, which is the Lagrangian. Taking the time integral means finding the general behavior of a system for a given time interval. Having T − U minimized is the meaning of the Lagrangian, because nature chooses the lowest energy state [7].

DIPOLES

What are Dipoles?

A dipole is an underlying concept of electromagnetism in physics. It can be described as the separation of positive and negative charges in atoms or molecules. This happens when there is an electric field inside the specified material, where the electrons and protons are shifted in opposite directions because of the repulsive force they experience [8]. It can also happen inside a current loop where a magnetic field is produced.

Therefore, there are 2 types of dipoles: electric dipole and magnetic dipole, respectively, according to their definitions, because they have a spatial orientation (i.e., position) in space, especially for moving electric dipoles that have trajectories [9], the term ”moment” is used as: electric dipole moment and magnetic dipole moment.

TRANSFORMATIONS ON A NEUTRON

Neutrons

Neutrons are electrically neutral subparticles in an atom’s nucleus. Therefore, its separation of positive and negative charges has been a research area in nuclear and particle physics. The electric dipole moment (EDM) of neutrons has not been observed in nature yet. The reason is that it would violate a fundamental symmetry in nature: charge parity symmetry (CP), its reason will be discussed in the following subsections [1].

Transformations

For the time being, in order to prove that the EDM for neutrons is not possible, it will be assumed that neutrons have EDM. In the following observations, if there is a violation, this assumption will be proven wrong, and it can be said that a neutron with EDM is not possible. An electric field and a magnetic field are applied to a neutron having an EDM (i.e., assumption). When the time transformation and parity transformation are also applied to this neutron separately, there are some observations regarding the electric and magnetic field, spin, EDM, and the energy of the neutron. When the time transformation is applied (i.e. the flow of time is reversed) the following phenomenons happen: the electric field stays the same; the magnetic field, spin, EDM, and energy (sign) change. When parity transformation is applied (i.e., spatial coordinates are reversed), magnetic field, spin, and EDM stay the same; electric field and energy (sign) change. Furthermore, it is known that the spin of the neutron and its EDM should align with each other. In Fig. 3, these transformations can be observed [1].

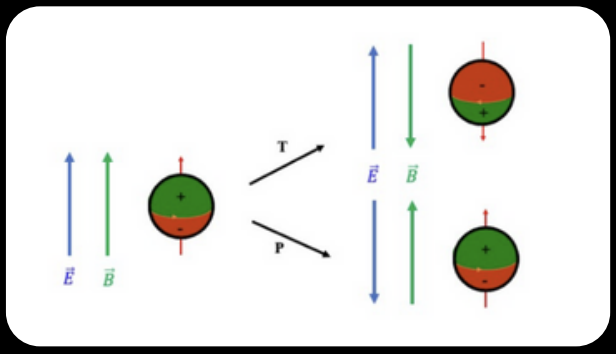

Fig 3. Transformations on a Neutron with electric or magnetic dipole moment: T is time transformation, P is parity transformation, red arrow represents the spin that is proportional to the EDM [1]

Hamiltonian

Hamiltonian is the total energy of a system described by the equation:

$$H = T + U \quad (2)$$

where T is the kinetic energy, and U is the potential energy. It should remain constant in a closed system because of the conservation of energy. The effect of time transformation on the energy of a neutron, which is given by its Hamiltonian, is described by:

$$H = -d \cdot E \quad (3)$$

where H is the Hamiltonian, d is the electrical dipole, and E is the electrical field [6].

CP PROBLEM

CP Problem

According to the equation (3), when the electric field changes (sign), for the Hamiltonian to stay constant, the EDM (sign) should also change. Conversely, when the EDM changes, electric field should also change. In the observations discussed in the "Transformations on a Neutron" subsection, it is observed that CP is violated according to the observations of time and parity transformations. The reason is that in the time transformation, electric field and spin (also EDM) behave oppositely: electric field stays the same but the spin; hence the EDM changes. In the parity transformation, EDM stays the same but the electric field changes. However, they should have both changed for the Hamiltonian to stay constant. On the other hand, the magnetic field and spin behave the same way in both transformations. Eventually, neutron EDM violates this but the magnetic dipole does not violate it. Therefore, the assumption is proven wrong. It can be concluded that neutron with an EDM cannot exist.

The θ parameter

The Lagrangian that describes how particles (i.e. gluons and quarks) interact through strong forces is given by the following equation with Einstein notation (μ, ν, α, β and a are repeated indices that refer to a summation):

$$\mathcal{L} = -\frac{1}{4}F^a_{\mu\nu}F^{a\mu\nu} + \sum_f \bar{\psi}_f(i\gamma_\mu D^\mu - m_f)\psi_f + \frac{\theta g^2}{32\pi^2}\epsilon^{\mu\nu\alpha\beta}F^a_{\mu\nu}F^a_{\alpha\beta} \quad (4)$$

Even though this equation looks complicated to fathom, the crucial part to notice is that the θ term parametrizes CP violation in this equation, because it is proportional to the neutron EDM, which was proven to violate CP symmetry.

However, in the experiments, this angle is found to be very close to 0 ($\bar{\theta} \lesssim 10^{-10}$) without a certain reason [1]. The solution to the problem on why it should be zero is the "Axion" solution, which was proposed by Roberto Peccei and Helen Quinn.

AXION SOLUTION

What is Axion?

Axion is the prime particle candidate for dark matter. The reason is that if the dark matter particle is a lowmass boson (i.e. force carrier), it may permeate the universe in a state which is cold, slow-moving and wavelike; similar to the axion's field [1]. It has a pseudo-scalar nature, indicating that it changes sign under a parity transformation. It is under the field of quantum chromodynamics (QCD), which is the study of the strong force interactions between quarks and gluons. According to the standard model, quarks are particles that constitute protons and neutrons, and gluons are the force carriers that bind quarks together. Axion is considered as a solution to the CP Problem. The axion field is proportional to the θ term, making the angle dynamic rather than a constant. The angle takes values between 0 and 2π. Because of the "spontaneous symmetry breaking" (which will be discussed in the following subsections) it undergoes, the θ term takes the value 0 every time and the neutron EDM vanishes. That is why axion is a solution to the CP Problem. In the equation (4), θ is taken as 0. Hence, the CP Problem is solved [1].

Some Symmetries

To introduce axion to the standard model, Roberto Peccei and Helen Quinn have proposed a symmetry: Pecce-Quinn (PQ) symmetry. This is a global axial U(1) symmetry, where the ”global” means symmetry transformation being the same everywhere and every time. ”Axial” means symmetry transformation acts differently on left-handed & right-handed particles, where the handedness describes the relative orientation of the particle's spin and velocity. Furthermore, U(1) symmetry transformation describes the symmetry where there is a rotation about a single axis. Axion is a field that obeys this symmetry [1].

Oscillatory Field

The axion field potential behaves periodically; its field is described by a cosine function as follows:

$$V(a(x)) \propto -\cos\left(\bar{\theta} + \frac{a(x)}{f_a}\right) \quad (5)$$

where V (a) is the axion potential, a(x) is the axion field, $\bar{\theta}$ is the CP-violating QCD vacuum angle (it is with a bar because it includes additional violating angles resulting from the quark mass matrix in addition to θ), and f_a is the axion decay constant [1]. It is assumed that the shape of the axion potential is described by the dilute instanton cosine-like gas approximation [10]. Instantons are quantum tunneling effects that give axions mass when they're scarce and not interacting with each other [11].

SOMBRERO POTENTIAL

What is Sombrero Potential?

Sombrero potential is a 2 dimensional polar coordinate analog to the:

$$sinc\,(x) = \frac{\sin x}{x} \quad (6)$$

function. This demonstrates its oscillatory property, which is related to the axion field. The reason why it is called ”Sombrero” is that it looks like a Mexican hat. This polar coordinate system valley has infinitely many equivalent minima points, which demonstrates its continuous symmetry. Sombrero potential is related to the “spontaneous symmetry breaking” of the axion field [1]. It is seen in the following figure (Fig. 4):

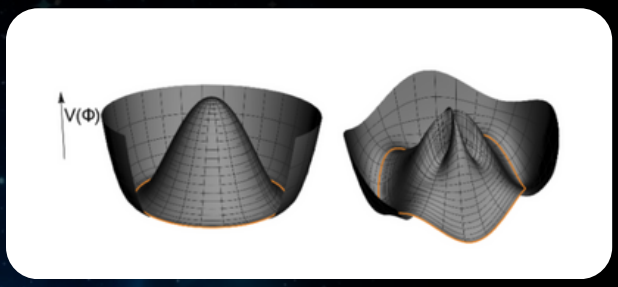

Fig 4. Sombrero Potential [1]

Spontaneous Symmetry Breaking

Spontaneous symmetry breaking can be illustrated using the parabola illustration: The vertex of a parabola lies on the axis of symmetry of the parabola. It is symmetrical with respect to the right and left sides of the axis of symmetry. If another point on the parabola is chosen other than its vertex, this point will not lie on the axis of symmetry. Therefore, the symmetry will be broken. Once the axion field picks one point on the orange ring in Fig. 4, it is called ”spontaneously broken symmetry”. Furthermore, the point is chosen to make θ=0 and choose the most stable point (i.e., where the energy is minimum). Since these minimum energy points are infinitely many, the field is continuously symmetric. When the field is pushed around the circle, the Nambu-Goldstone boson, which is an axion, emerges as a result of the broken symmetry. In the following section, scenarios

concerning when and how axion dark matter occurred will be discussed [1].

EARLY UNIVERSE AND AXION

Introduction

In the early universe, the universe was flat, high in temperature, homogeneous, and isotropic, meaning that its properties were independent of the direction from which it was measured [12]. According to Friedmann, temperature was at its maximum at the beginning of the Big Bang. The scientists have proposed two scenarios for the origin of axion dark matter [1].

Scenario 1

One of them investigates the time before the Big Bang. In this scenario, the universe is homogeneous and smooth. Axion's evolution is only dependent on the wave equation of the universe expanding. As the universe keeps on expanding, the axion field oscillates. Over time, these oscillations dampen, hence the energy decreases. This damping turns into axion dark matter [1].

Scenario 2

The other scenario concerns the duration of the Big Bang. In this scenario, the axion field may not be the same everywhere. This is because of some cosmic strings, which are topological, thin, line-like defects. They emit gravitational waves and carry energy. Another reason is the existence of domain walls. They are sheet-like structures. They separate two regions of space where a field settles into different vacuum states.

Considering these phenomena, because of the axion field compositions that appear between regions where the axion field has dissimilar values, this axion field may decay into axion dark matter [1].

CONCLUSION

In this article, dark matter, the expansion of the universe, the CP Problem, and its axion solution have been examined. Axion is one of the most prominent theories as a candidate for dark matter. It is related to the fundamental symmetries in the universe. Its relation to cosmology and the early universe gives rise to two different scenarios: the axion's origin before or during the Big Bang. There are many experiments to understand dark matter and its relation to the axion. The microwave cavity haloscope is an example designed to detect axion dark matter by converting axions into photons when a strong magnetic field is present [1]. Even the axion's mass is not known very accurately because of the limitations of equipment, time, and resources. However, by interconnecting interdisciplinary approaches using engineering and other areas, it is believed that this research area will continue to improve.

ACKNOWLEDGEMENTS

I would like to thank my advisor Assistant Professor Deniz Aybaş for her assistance and support throughout this article.

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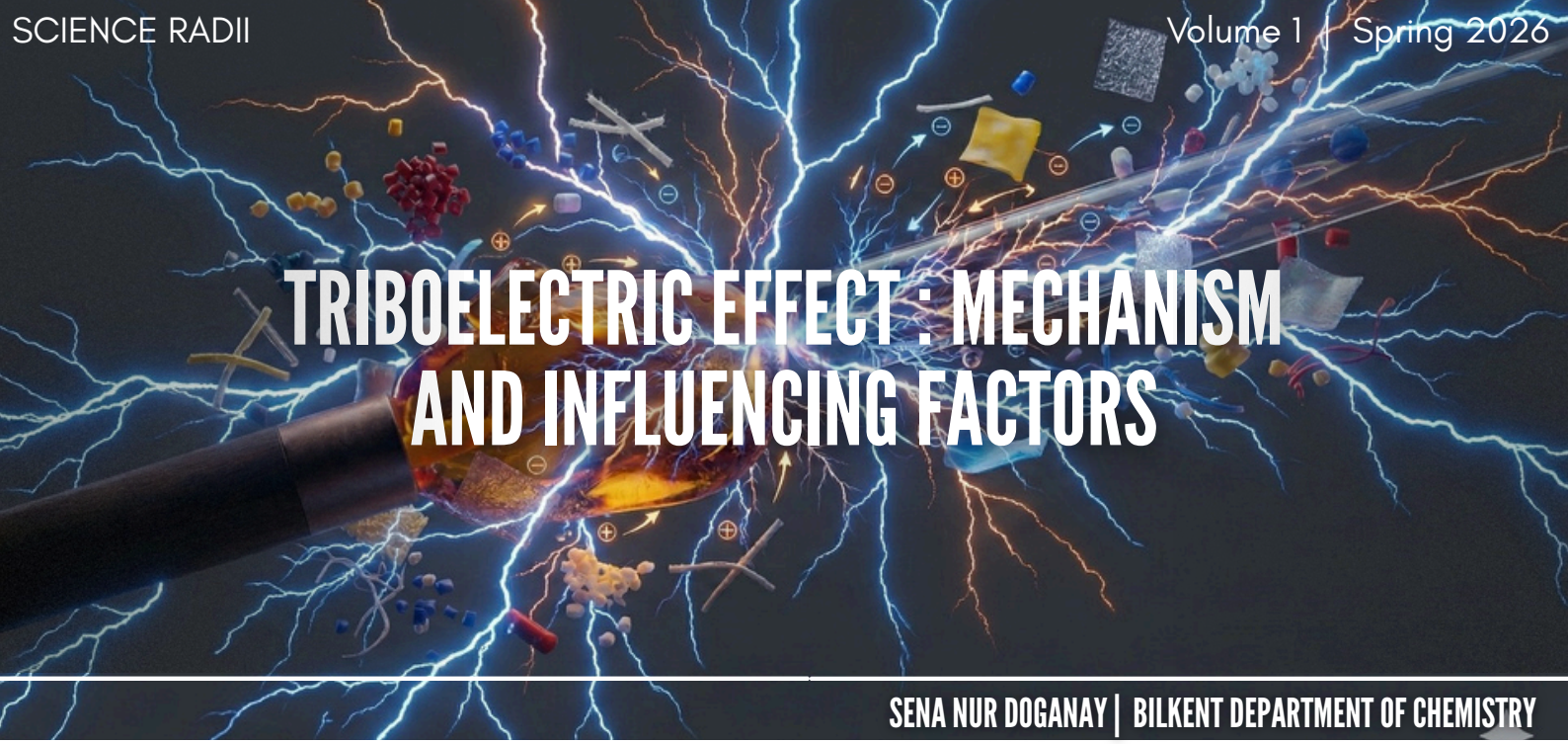

TRIBOELECTRIC EFFECT : MECHANISM AND INFLUENCING FACTORS

SENA NUR DOGANAY | BILKENT DEPARTMENT OF CHEMISTRY

The riboelectric effect, which is generated by the connection and separation of materials, is a fundamental concept of daily life. There are various causes of tribo-electric effect like electron, ion, and material transfer. In addition, environmental and material properties can impact triboelectric charges.

Introduction

When two different surfaces are contacted and then separated, transfer of electrons creates surface charges. This is called the “triboelectric effect”. The concept of triboelectricity dates back to ancient times. One of the Greek philosophers, Thales of Miletus, realized that rubbing amber against wool was creating charges on the substances. Moreover, “tribo” means “rubbing,” and “electric” comes from the Greek word for amber, “elektra”. Thus, “triboelectric” in Greek literally means “rubbing amber” [1].

People frequently encounter examples of the triboelectric effect in their daily lives. When a plastic balloon is rubbed against hair, the hair becomes statically charged, causing it to lift and stick to the balloon. A pencil that has been rubbed on hair beforehand can attract small pieces of paper. These are just a few daily life examples of the triboelectric effect.

Although the triboelectric effect may seem very simple at first, this concept involves deep knowledge of chemistry and physics. Atoms do not lose electrons easily, and gaining an electron from one neutral atom needs energy. However, electron transfer occurs with the triboelectric effect by contact and separation rather than requiring high amounts of thermal or electrical energy. This raises the question of how simple rubbing can lead to electron transfer, resulting in the triboelectric effect.

Atoms consist of protons, neutrons, and electrons. Protons have positive and electrons have negative charges. Electrons are not localized, so they can transport charges, which means an excess or a deficiency of electrons [2]. Electrons move from one surface to another, and this leads to one surface having an excess of electrons and the other being deficient of electrons for triboelectricity. The excess and lack of electrons create a negative and a positive charge, respectively. This makes up the core mechanism behind the triboelectric effect. Rubbing is not essential for this effect to occur; the connection and separation are enough to create a triboelectric charge between the two surfaces. Generally, the potential differences between surfaces are extremely small.

However, a potential difference in a very close range can create an electric field large enough to move electrons through the electric breakdown of air, which causes sparks associated with static electricity [3]. Although the physical mechanism of electron transfer is widely discussed in the physics literature, several alternative interpretations exist. Different perspectives highlight that triboelectricity cannot be fully explained by a single discipline.

Electron

Electrons play a significant role in the triboelectric process because they create charges. surface W is an important factor which determines the minimum thermodynamic work that is needed to be done in order to remove an electron from the surface to the vacuum level. Surface W demonstrates the ease of losing or gaining electrons during contact and separation.

$$W = E_{vacuum} - E_{fermi} \quad (1)$$

E_{fermi} shows the "Fermi level". The Fermi level demonstrates the highest occupied electron energy level in the solid at 0 K [4]. It represents the top of the filled electronic states and acts as the reference point in the work-function formula. When two materials with different work functions are contacted, electrons move from the material that has a smaller work function to the material that has a larger work function. Fermi levels of both surfaces go to an equilibrium, and the differences become zero. After separation, the physical electron path is broken, so electrons cannot go back to their original positions. Two materials have opposite charges [5].

The primary force that leads to electron transfer in triboelectricity is the difference in work function. The secondary effect can be explained by the phonon-electron system [6].

The phonon-electron system demonstrates the phonons' impacts on electron behaviours through solids. In solids, electrons go through a crystal lattice, which consists of vibrating atoms. Vibrations are called "phonons".

When electrons move, they interact with these vibrations, phonons, and it is called phonon-electron interaction. Electrons make interactions with phonons through probabilistic scattering. It states electrons do not interact with vibrations at fixed. Each interaction occurs with a certain probability, which depends on temperature and lattice vibrations. Phonons influence the likelihood of electron transfer to occur by raising or lowering the barrier locally. In the triboelectric effect, electron-phonon interaction can resist or allow charge transfer between surfaces [7].

An electron can move through a small tunnel by absorbing or emitting phonons, thereby overcoming energy barriers. This is called "quantum tunneling". Phonon interactions can assist or hinder quantum tunneling at specific moments by lowering or raising the energy barrier, but they do not necessarily cause it. Quantum tunneling occurs because the wavefunction of the electron extends to the other side of the barrier; therefore, it also has a probability to exist on that side. Thanks to quantum tunneling, electrons can transfer from one surface to the other even if they do not have enough energy to overcome the energy barrier required for the transfer [8]. Both phonon-electron interaction and quantum tunneling might provide electrons to move from one surface to another surface with less energy and significant factors on the triboelectric effect, especially at the nanoscale.

ION

Although electron transfer is the primary source of triboelectric effect in the solids, ion transfer also provides triboelectricity, particularly in a liquid interface. In such a case, ions contribute to triboelectricity rather than electrons. In insulating materials charge formation is limited because of a lack of free charges, but can still occur. While the surface is strongly bound by one charge polarity, it is loosely bound by other ions with the opposite charge on the insulator surface. This circumstance leads to an imbalance of affinity with various ions. During tribological contact, a particular type of ions is transferred so charge accumulates on the insulator surface [6]. In the case of conductors, free electrons exist on and inside the surface; therefore, ions are not the dominant charge carriers. However, if the interface between the conductor and the environment is a liquid or a polymer, triboelectric charging can occur. Ion transfer occurs at the interface between the conductor and environment (or another surface). During the connection, ions can be attached to (adsorption) or detached from (desorption) the conductor's surface. Two layers form between the surface and environment, where one layer of ions is present on the conductor surface, and the other layer, which carries ions of an opposite charge, is formed on the opposing surface. Two different layers occur, which are called the “electric double layer (EDL)”. While a layer of ions exists on the liquid surface, the opposing surface acquires the opposite charge. When the surfaces are separated, some ions remain trapped, which creates a triboelectric potential [9].

Material

Besides ion and electron transfer, material transfer may also contribute to the formation of triboelectric charges. Strongly rubbing both surfaces against one another and applying pressure on the surfaces can transfer small pieces of both surfaces to the other. Transferred material might provide a charge imbalance. Therefore, dynamic changes such as strain can cause the material transfer because substances tend to exist in lower energy states. Dynamical factors change the potential energy of the surface, and the materials that tend to go to lower energy states might be transferred [6]. This contributes to the triboelectric effect. Additionally, studies on polymers such as PDMS have shown that triboelectric contact can involve homolytic and heterolytic bond breaking [10]. A chemical bond consists of two electrons. While a bond is breaking, bond electrons can separate equally, which is called “homolytic bond cleavage or unequally, which is called “heterolytic bond cleavage”. After homolytic and heterolytic bond breaking, some ends of the polymer chain open. These open chain ends are more chemically reactive and can react with new functional groups, resulting in a surface charge.
Consequently, contact electrification may involve the transfer of these charged material patches between surfaces. This situation contributes to the formation and persistence of triboelectric charges [10].

Triboelectric Series

In 1757, the Swedish physicist J. C. Wilcke created an empirical list of materials. He ordered materials according to their tendency to acquire positive/negative charges by mechanical connection. After that, many scientists prepared their material lists according to the willingness of each material to acquire charges.

In 1917, Shawn first used the term "Triboelectric Series (TS)". It is a simplified material table that shows their tendencies to gain or lose electrons after physical connection. It is still a controversial matter, and there is no universal version that is accepted by all scientists. Although this table is empirical and context-dependent, it contributes significantly to the knowledge we have about solid surface properties and experiments about triboelectricity [11].

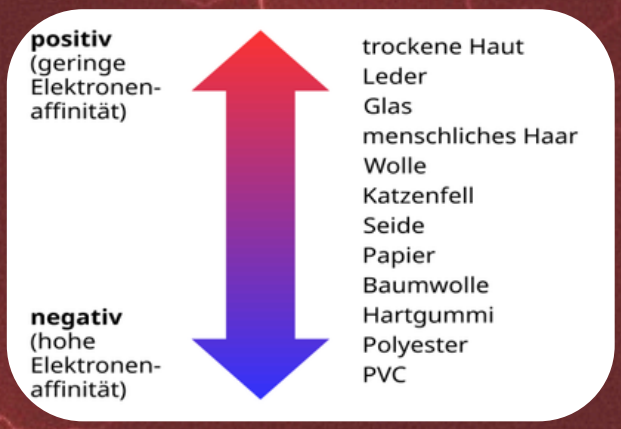

Fig 1. Triboelectric series showing materials ordered by their tendency to gain or lose electrons. Adapted from MikeRun, Wikimedia Commons, CC BY-SA 4.0. [12]

Factors Impacting Triboelectric Effect

Both surface properties and medium are the main factors that can influence the triboelectric effect. Although the type of material is the most noteworthy contributor to the triboelectric effect, there are other contributors. Surface roughness determines the contact area between the materials; rougher surfaces increase the area of contact, which in turn increases charge transfer. Additionally, particle size is also a significant factor. When two particles are contacted, they gain opposite charges. Latest studies demonstrate that statistically, while larger particles tend to have positive charges, smaller particles tend to gain negative charges. Stress, humidity, and acidity are environmental changes. The ability to create ions and electrons by stress is proven. Furthermore, stress load can change charge transfer mechanism and their behaviours, so the triboelectric effect is impacted by stress directly.

Both acidity and humidity can create ions, so they can change electrical conductivity. During tribo-contact, salt or water molecules are attracted to the surfaces and create a conductive layer. This conductive layer or film allows charge leakage to occur between the two surfaces, therefore the overall charge decreases. [6].

Charge Transfer Between Identical Materials

When two identical materials are contacted, common sense does not expect charge transfer between them. However, charge transfer does occur. A significant factor that impacts charge transfer is symmetry. If identical materials are also perfectly symmetrical, the charge transfer direction is completely random, so surfaces may have the same or opposite charges. If substances are not symmetrical, charge transfer tends to occur in a preferred direction and surfaces become oppositely charged [13]. If the charges of surfaces are not in equilibrium, charge transfer occurs from the higher non-equilibrium charge surface to the lower non-equilibrium charge surface. Additionally, the net charge transferred is proportional to the difference in surface charge density [6].

From a chemical perspective, small differences in surface composition can create regions that act like a charge acceptor or a charge donor. During contact, chemical bonds can break either equally (homolytic cleavage) or unequally (heterolytic cleavage). Breaking bonds can generate open-chain ends on polymers. Reactive open ends can provide ions or radicals by reacting with these. Open ends, radicals, and ions cause electron density differences.

Electrons can accumulate at particular regions, and other regions may have an electron deficiency. This leads to the formation of local charge regions, which are called "charge mosaics" [10]. These charge mosaics allow charge transfer between identical materials.

Conclusion

The triboelectric effect arises from electron, ion, and material transfer, which causes a charge imbalance. Several factors can impact triboelectricity by decreasing or increasing the amount of charge transferred. Interestingly, triboelectric charge transfer occurs between identical materials when the surfaces are asymmetric or the charges are not in equilibrium, but also between materials that have different work functions or surface properties. The triboelectric effect and its mechanism provide scientists with valuable insights into material behaviour, which leads to practical applications and experiments, so the triboelectric effect is one of the most significant concepts in material science.

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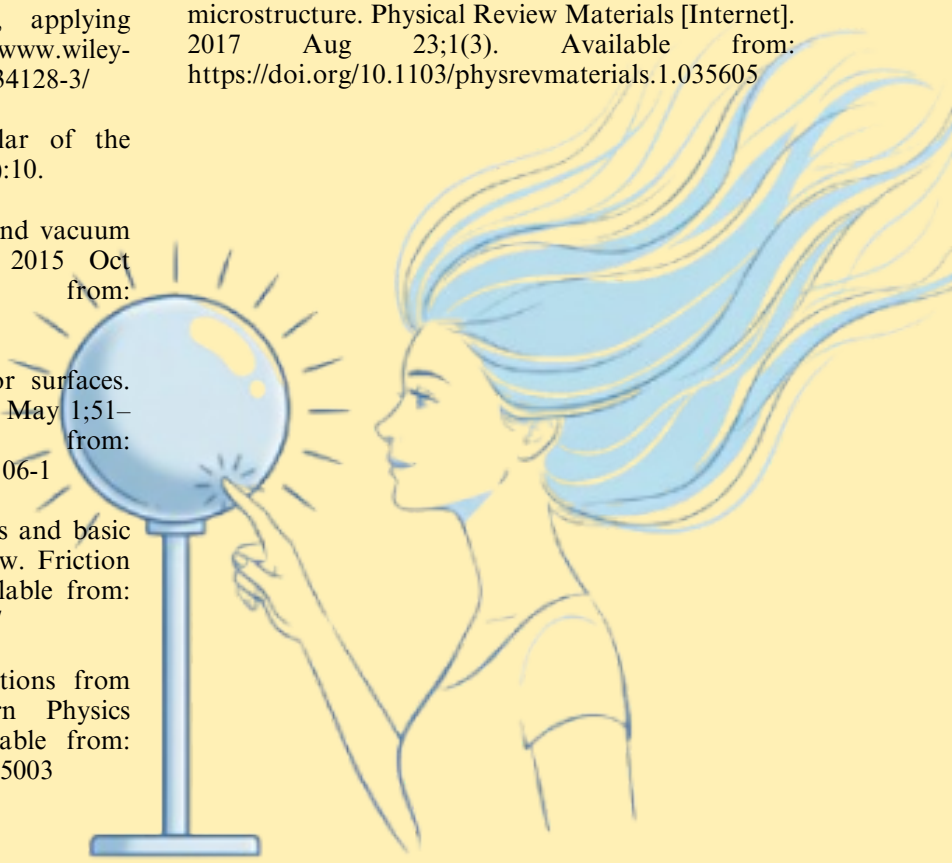

A New Chapter in The World of Painkillers

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Pain is one of the most critical signals in our body that keeps us alive. Although it is crucial for survival, it is an unpleasant feeling that disturbs people throughout their daily lives. Pain is a familiar feeling to every human being on this planet, and it can be defined as discomforting emotional and sensory experiences [1]. To reduce the pain, most people use different types of painkillers.

Opioids are one of the most commonly used classes of painkillers and are synthetically produced. The most well-known examples of opioids are morphine and heroin. Opioids are used in acute pain treatments, and their working mechanism is based on their interactions with opioid receptors. Opioid receptors are a class of G protein-coupled receptors (GPCRs) that are responsible for the transfer of information coming from nociceptive receptors. In these pathways, opioids act as inhibitory agents. They affect both afferent and efferent pain pathways by decreasing the release of neurotransmitters. Thus, they inhibit the flow of information and reduce pain [2]. Opioids are effective drugs, and they work well in theory; however, in real-life usage, they are highly addictive drugs even in the short term. This is because they activate the brain's strong reward centers and trigger the release of endorphins, which are neurotransmitters that produce a sense of well-being. Today, opioid addiction remains at an epidemic level worldwide [3].

As an alternative to opioid drugs, in January 2025, the U.S. Food and Drug Administration (FDA) approved a novel non-opioid painkiller. This new drug is known as suzentrigine with the market name of "Journavx" [4]. Journavx's action mechanism depends on voltage-gated sodium channels on pain-sensing nerve cells. These Na+ channels are responsible for generating electrical signals, also known as action potentials, in response to pain. Then, this action potential is transferred to the related regions of the brain, and pain perception is completed. The human nervous system has ten subtypes of voltage-gated sodium channels, and old technology

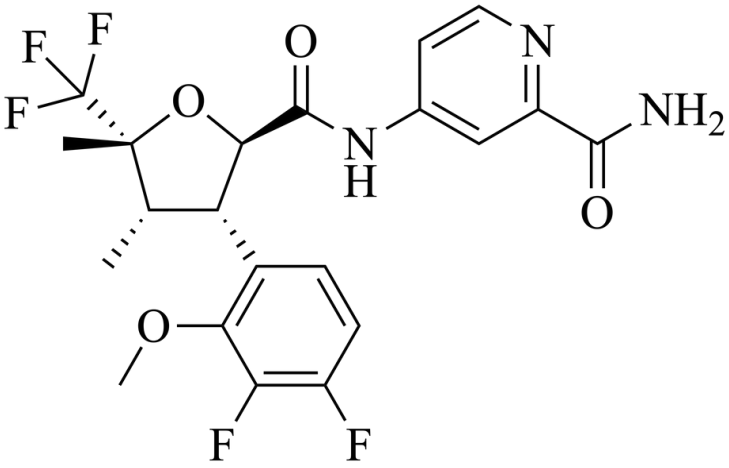

Figure 1. Chemical structure of suzentrigine

drugs such as local anesthetics block all of them. As an alternative, Journavx targets one of the most important subtypes: NaV 1.8 [5]. This receptor is exclusively found in peripheral sensory neurons, also known as nociceptors, and this feature makes it a promising target for pain inhibition with minimal side effects. Journavx binds to the channel's second voltage-sensing domain (VSD2) and inhibits the activation. This is a different approach compared to that of old drugs that directly block the pores of the channels. Journavx's mechanism works regardless of neural activation and thus can be effective in many situations. Additionally, since it works on a specific Na+ channel, it does not trigger a reward mechanism like opioids, and this reduces the risk of developing an addiction [5].

In summary, Journavx is a new alternative to the commonly used opioid painkillers. Unlike the opioids that act on GPCRs, Journavx directly acts on a specific Na+ channel in nerve cells responsible for pain sensing. This novel mechanism has the potential to represent a paradigm shift in pain treatments, with the expectation of pioneering many new drugs. Unlike opioids, the risk of addiction is extremely low in the use of Journavx; it offers hope and relief instead of a life full of addiction. Rather than being another painkiller that is destined to be lost in the crowd of countless painkillers, it may be the beginning of a new age in how modern medicine treats pain.

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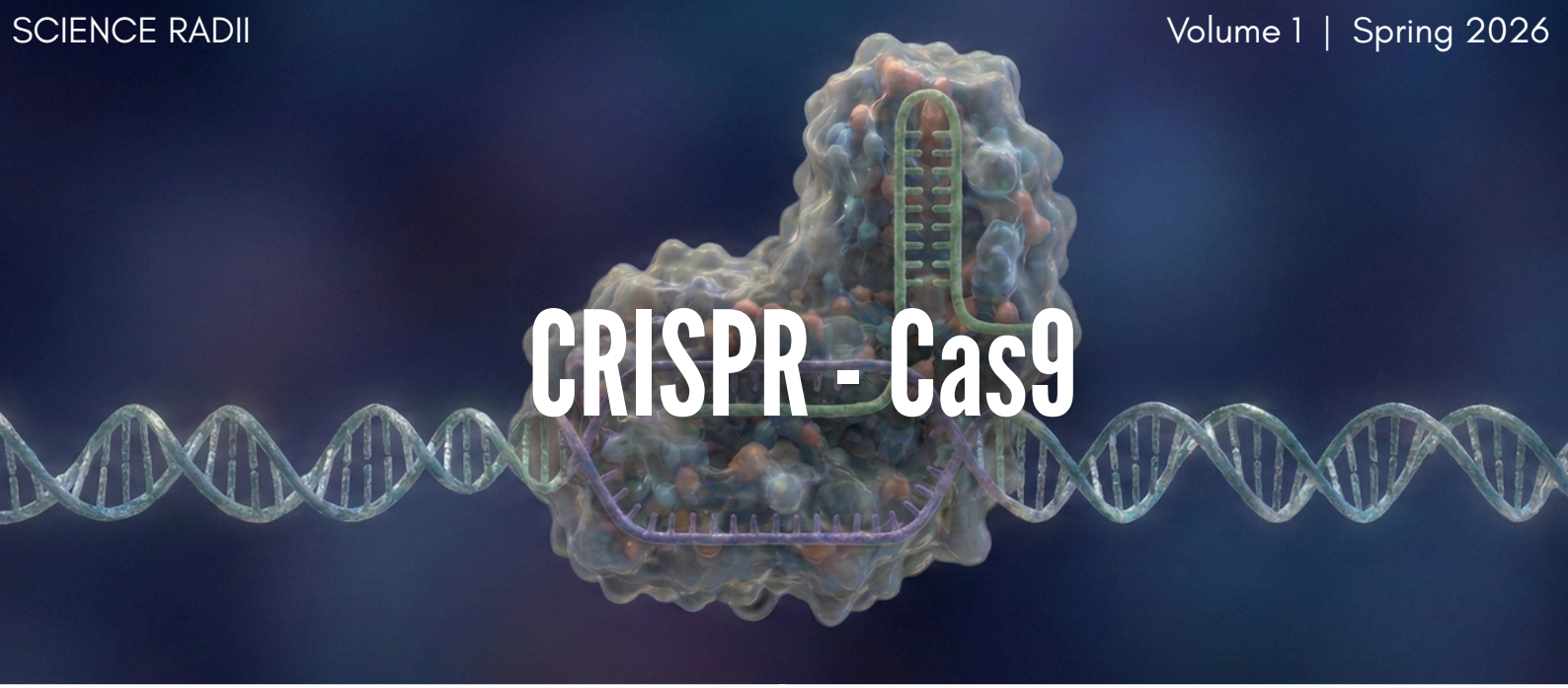
DID YOU KNOW?

Dr. House, the famous grumpy doctor that we all recognize from his medicine box, actually uses an opioid. It is called hydrocodone, or as you may remember, Vicodin. No wonder he's always cranky- in addition to solving medical riddles, he is also searching for his next dose!



CRISPR - Cas9

EKIN SEZEN | BILKENT DEPARTMENT OF MOLECULAR BIOLOGY AND GENETICS

Genome editing is an approach that allows making precise alterations in an organism's DNA, allowing researchers to add, remove, or change the genetic code for genetic studies, treatments, enhanced agricultural efficiency, and biotechnological studies. Targeted nucleases are powerful, commonly used tools for such genome editing processes. They are frequently used due to their precise binding ability to target sequences. Among all the tools, the CRISPR-Cas9 system stands out for several reasons. It offers a highly effective tool that is specific, simpler to design, and supports large-scale, simultaneous editing, compatible with many different cells [1].

What is CRISPR-Cas9? Its Origin and Mechanism

CRISPR (clustered regularly interspaced short palindromic repeats) is a specialized DNA sequence initially discovered in bacteria. Together with CRISPR-associated (Cas) proteins, this system provides defense against plasmid uptake and phage infection. The development of the CRISPR adaptation module was crucial for the evolution of prokaryotic adaptive immunity, allowing bacteria and archaea to store short fragments of foreign DNA from previous infections as spacers within their CRISPR arrays [2]. These short fragments of the invaders' DNA allowed the prokaryotic organisms to repair their genome by excising the foreign sequences, which are identified by the spacers. The CRISPR system is divided into two classes according to the differences in core Cas proteins, and each of the classes contains three subtypes with different proteins [3]. While some classes work on DNA, there are other classes that can work on RNA molecules. Among the second class, the type II system uses the Cas9 protein, an enzyme that works together with CRISPR to cut DNA at specific sites, thereby clearing integrated viral sequences. After the invasion of a phage, some of the genetic sequence of the invader gets integrated into the host's genome. After integration, the adaptation of the CRISPR system is initiated with the recognition and targeting of a foreign sequence, followed by the acquisition of this DNA and its integration as a new spacer into the CRISPR array [4]. This CRISPR array is made up of alternating repeats, originating from the host's genetic material, and spacer

sequences derived from the invader. Spacer sequences are non-coding pieces in between genes; in the system, they are placed between repeats and allow the system to identify specific sequences of foreign DNA. The mechanism used by scientists for genome editing is a repurposed version of the same mechanism found in bacteria. As Jiang and Doudna [5] note, the RNA-mediated targeting system can be manipulated using single-guide RNA libraries to pinpoint drug-target or disease-resistance genes in the genome, allowing quick assignment for drug targets.

Working Mechanism

The CRISPR system has three main stages in its working mechanism. The first step of the CRISPR-Cas9 working mechanism is recognition of the sequence to be cleaved. At the 5' end of the CRISPR RNA, there is the spacer sequence that complements the foreign genetic material, while at the 3' end, it contains a CRISPR repeat sequence. The repeat sequence does not directly target the DNA, but instead helps maintaining of the structure of precursor RNA. Using the spacer and its complementary target sequence, Cas nucleases can initiate cleavage of a specific sequence. Therefore, in the absence of single-guide RNA, the complex remains inactive.

The second step is cleavage. "The Cas9 nuclease makes double-stranded breaks (DSBs) at a site three base pairs upstream to PAM. The PAM sequence, standing for protospacer adjacent motif, is a short 2–5 base pair in length conserved DNA sequence, downstream of the cut site. The most commonly used nuclease in the genome-editing tool, Cas9 protein, recognizes PAM at 5′-NGG-3′ sequence where N can be any base. Once the Cas9 has found a target site with the appropriate PAM, it triggers local DNA melting followed by the formation of an RNA-DNA hybrid" [6]. After cleavage, the last step is the repair of the cut DNA. After the Cas9 complex disassociates from the strand, the DNA is induced to a double-strand break. The host cell's endogenous repair machinery detects this double-strand break and repairs it.

"These repair pathways include homologous recombination (HR), classical non-homologous end joining (cNHEJ), microhomology-mediated end joining (MMEJ), and single-strand annealing (SSA)" [7]. The first and most precise method is homologous recombination, which uses a homologous DNA template to lead the repair using either single-or double-stranded DNA molecules. The non-homologous end joining method recruits proteins that join the ends without any additional sequence. While it is fast and effective, it frequently leads to small, random mutations in the sequence. The Microhomology-mediated end joining method resects the broken ends of DNA until it finds small matching sequences, then ligates the ends from these sequences. The Single-strand annealing method also uses homologous repeats to ligate double-strand breaks. However, while the classical non-homologous end joining method requires only 1–4 nucleotide-long homology, microhomology-mediated end joining requires 1–16 nucleotide alignment, and single-strand annealing needs a wider alignment caused by directly repeated sequences. [8].

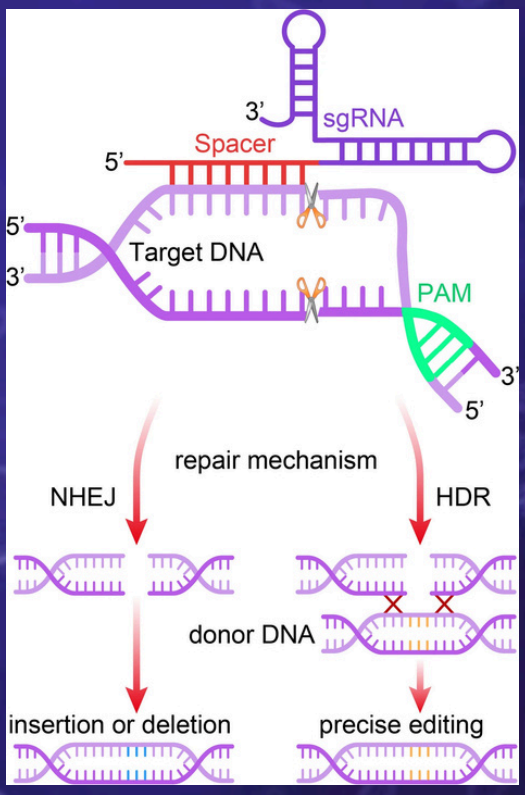


Figure 1. Recognition of target DNA is followed by the two repair mechanisms [9].

Upon recognition, and cleaveage steps, the double strand break is repaired using Non-Homologous End Joining via insertion or deletions, or by Homology Directed Repair that uses another DNA molecule as template [9].

Limitations of CRISPR-Cas9

While its cornerstone effect in genetic research and therapies cannot be underestimated, this method still has some limitations to overcome in order to achieve wide use [10]. The first being the off-target effects. When the tool is used for gene therapy, it has a high frequency of off-target effects [10]. Off-target effects on the topic are "deposition of unexpected, unwanted, or even adverse alterations to the genome" [11]. While these can be overlooked for some agricultural and educational studies, their effects on critical processes like treatment-purposed genome editing set a great limitation for approved usage.

The second limitation of the technique is that it requires a protospacer adjacent motif (PAM) alongside the target. Short canonical PAM recognition sites such as SpCas9 can be large and hard to pack into adeno-associated virus vectors, whereas SaCas9 (ortholog of SpCas9), which can be packaged more easily, can have longer PAM sequences. These problems narrow the therapeutic windows [10]. These create limits as desired sequences might be absent in the desired loci.

Another problem with this method is the immunogenic toxicity. The majority of humans are already immune to the standard CRISPR-Cas9 proteins. As discussed by Charlesworth et al [12], analysis of human serum reveals that a significant majority of the population carry a pre-existing adaptive immune response to Cas9 proteins, detecting both antibodies and specific T-cells against SaCas9 and SpCas9 in most donors. These findings can get in the way of common usage of the technique until technology advances toward the immune rejection problem in clinical applications.

Lastly, some ethical problems can arise during genome editing applications to germline or similar cell groups. Since changes in the genome can be carried on in generations, off-target effects can get even larger with accumulating mutations and crossing-overs. Furthermore, if these tools start to be used more frequently, children of families with access to higher technology treatments and the ability to cover their cost will have an unfair genetic advantage over other children.

Advantages of CRISPR-Cas9 Compared to Other Genome Editing Methods

One of the genome editing methods which can be used for similar applications is the Zinc Finger Nucleases (ZFNs). Zinc finger nucleases are programmable DNA-cutting enzymes that enable gene-targeting for targeted mutations or gene replacements [13]. Similarly, Transcription Activator-Like Effector Nucleases (TALENs) can be used. TALENs consist of two units as a non-spesific DNA-cleaving nuclease and a DNA binding unit to enable targeting [14]. The increasing potential for usage of genome editing tools, including CRISPR-Cas9 grows larger with advancements in the science field.

Some of the advantages Crispr-Cas9 mediated genome editing include a fast and flexible design. As we have discussed earlier, specific PAM sequences can create problems for the designing process; but new sequences are being discovered each year that have flexibility for sequencing (some have non-certain nucleotide sequences and can work with any of the four nucleotides).

As a second advantage of using CRISPR technology, its cost-effectiveness can be shown. CRISPR-Cas9 can offer significant financial efficiency compared to other gene manipulation tools, such as zinc finger nucleases and transcription activator-like effector nucleases (TALENs) that require protein engineering [15]. These older methods can be expensive preventing large-scale applications as they require custom proteins for each specific target, combined with a validation for the whole complex. In contrast, CRISPR system require only an RNA guide which can be fetched from a RNA library. This programmability reduces the time it takes to design and produce, costs, and trained specialist need to a certain extent.

Applications of CRISPR/Cas9

There are many potential usage areas for this relatively new genome editing tool. One of its most common uses is in gene therapy and the treatment of diseases and disorders that have a genetic foundation. CRISPR can correct mutations that cause diseases such as sickle cell anemia, cystic fibrosis, and cancer. Another use of it can be for infectious diseases. Rather than changing the patient's genome, the tool can directly target the virus itself.

When used in agriculture, the tool can also be used to enhance security, nutrition, and yield by modifying genes known for affecting these traits. The agricultural use can enable plantation with disease resistance and climate resilience that can enhance sustainability.

Some industrial applications of genome editing enable changed genomes for algae and yeast, and usage of them for producing lipids and alcohols, or plastic-digesting organisms.

CRISPR is not only an active tool for changing the genome but also for understanding it. Scientists can use it to study the functions of genes, model diseased organisms, and test newly developed drugs and therapies.

Did you know?

The 2020 Nobel Prize in Chemistry was awarded to Emmanuelle Charpentier and Jennifer A. Doudna for the discovery of the CRISPR/Cas9 genetic scissors.

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THE BILIBILI CORNER

You are Counting Time Wrong (But So Is Everyone Else)

AHMET EMIN CEYLAN

We count almost everything in tens, but we measure time in twelves. It seems strange. Why don't we have a 10-hour clock or maybe just a 5-hour clock? Wouldn't it be easier to divide it that way? The answer is not far away; it is literally in your hands.

We usually count "one, two, three" with our fingers. But ancient people in Egypt and Sumer used a different, shrewd method. They used their thumb to tap the three joints of their other four fingers. If you try it now, you will see: three joints on four fingers equals twelve. It’s simple math, 3*4=12.

Of course, this system didn’t survive only for its convenience. Another reason is math. The number 10 is actually quite limited because it is just the product of two prime numbers. You can merely divide it evenly by 2 and 5. The number 12 is much more flexible than 10. You can divide it cleanly by 2, 3, 4, and 6.

This feature made it ideal for experts such as astronomers and clockmakers. They could split the day into halves, thirds, or quarters without dealing with difficult fractions. So, while our money and many other things use the base-10 system, our clocks are stuck with the more useful base-12.

GEOMETRICAL ORDER IN NATURAL RANDOMNESS: LIESEGANG PATTERNS

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In the late 19th century, a German chemist and photographer achieved an interesting outcome with a simple mistake. He accidentally droped a few drops of silver nitrate solution onto the gelatin with potassium chromate. After a while, he observed the diffusion of the silver nitrate solution into the gelatin gel with dissolved potassium chromate, and surprisingly, obtained patterns that geometrically repeated themselves [1]. Those patterns were named after Raphael E. Liesegang, and thus, the first concrete step into the fascinating world of patterns was finally taken by accident.

Despite their late discovery, Liesegang patterns have already been in the real world, demonstrating that self-assembly systems have existed for centuries. For instance, colony developments of various bacteria, such as Bacillus (B.) subtilis, exhibited a typical concentric ring structure, similar to Liesegang patterns [2]. The bacterial colony was shaped by the impact of agar gel and nutrients that the bacteria needed to live. Additionally, Liesegang patterns were still visible in the culture medium. Thus, destroying such a ring-like life pattern altered cell metabolism, allowing Liesegang patterns to occur naturally among them [2]. Furthermore, following the discovery of the Liesegang phenomenon, geologists began to take it into account. Rocks are examples of such patterns that can emerge in nature. The analogies of Liesegang-type periodic patterning on the rock structures themselves raised a question of the origins of the various rock systems [2]. Mimicking natural systems with related chemicals leads to the development of models and laws that can be applied to these systems. In other words, the patterns that have existed for centuries partially preserve their mystery.

Liesegang patterns can also be produced in artificial settings, just like Raphael E. Liesegang did. They can be generated in 1D, 2D, or 3D, and remarkably, he first encountered the two-dimensional example with silver chromate by accident, as mentioned. Experimentally, tiny test tubes are preferred for 1D and petri dishes are proper choices for 2D samples. Cubes or spheres are mainly used for 3D sample preparation [3]. The chemistry behind this reaction-diffusion system can be enlightened by examining the chemistry of the components.

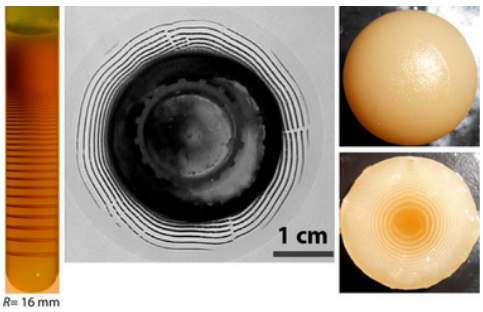


Figure 1. Respectively, One-Dimensional, Two-Dimensional, and Three-Dimensional Liesegang Patterns [3].

THE KEY CONCEPTS FOR UNDERSTANDING

Since the Liesegang phenomenon depends on familiar and basic concepts, all of them should be considered in detail. The logic behind such random systems can be clarified by revisiting and addressing related concepts, because in some cases, like this one, the complex ones are often hidden in the basics. Liesegang patterns are typically described as a specific type of reaction-diffusion system, implying that two distinct yet related principles are at play [3]. Diffusion is the spontaneous movement of molecules, atoms, or ions from areas of higher concentration to regions of lower concentration. Diffusion does not require any external energy; therefore, it is an irreversible process [4]. Moreover, the 'reaction' near the diffusion refers to the precipitation since the pattern bands are formed by the precipitation of ions in the system. To understand such reactions, a new subject emerges: solubility.

Solubility seems familiar yet essential, shaping the destiny of Liesegang patterns. As an easy-to-understand explanation of such concepts, a solution is a homogeneous mixture of two or more substances. Solvent is a significant solution component; it is present in large quantities compared to the others, whereas the solute is the matter dissolved in the solvent. The dissolution process is observed when the solute or solutes disperse homogeneously in the solvent and stabilize through interactions to form a solution [4]. Solubility determines the maximum amount of solute that a solvent can dissolve. Particularly, the solubility limits of most salts and compounds have been established by considering the pressure, temperature, nature of the solvent and solute, etc. These determinate limits are essential to follow the reaction because precipitation begins when the solubility limit is exceeded.

Chemical precipitation is the process in which ions or molecules in a solution form a precipitate with significantly low solubility under suitable conditions [5].

When a solution contains more solute than it can dissolve, it becomes unstable and supersaturated. If that solution reaches the solubility limit, it gathers and forms a precipitate. The solubility limit is the key to this process because it marks the exact point at which precipitation begins. In other words, precipitation is quantitatively followed by concentration using the solubility product constant, Ksp [5]. Therefore, the concentrations of free ions become variables in this process when the instantaneous product of ion concentrations of a sample reaches the Ksp value; precipitation begins.

Although Liesegang patterns form randomly by simultaneous diffusion and precipitation, they follow a periodic rule: a geometric series. A geometric series (Sn) is the ratio of each two consecutive terms of the series, which is a constant function [6]. Namely, the consecutive terms are proportional to each other. Considering an is the nth term of the series, and r is the constant ratio, the general empirical formulas are given below [6]:

$$S_n = a_1 + a_2 + a_3 + \ldots + a_n \quad (1)$$

$$S_n = a_1 + r.a_1 + r^2.a_1 + \ldots + r^{n-1}.a_1 \quad (2)$$

$$\frac{a_2}{a_1} = r \quad (3)$$

REVISITING CONCEPTS

In Liesegang pattern formation, two solutions with different media are used. The outer medium consists of only ions dissolved in distilled water, whereas the inner medium comprises a gel (hydrogel) that can retain water and dissolved ions. In other words, the inner medium has a more compact structure. So, Liesegang systems combine the two systems and the diffusion between them. Therefore, water is a liquid solvent; however, hydrogels are different. Hydrogels consist of water and gel matter, which mostly have a polymer web structure, being smooth but not fluid, allowing them to exhibit distinctive chemical and physical properties.

They are not completely liquid or solid, but rather have a gel-like consistency, similar to soft matter that can be easily shaped or molded without complex processes [7]. Additionally, their three-dimensional crosslinked polymer network renders them more solid than a liquid; however, their ability to retain water imparts flexibility and softness [8]. Namely, the gel medium is more compact than the aqueous solution, leading to a diffusion-controlled precipitation process.

In regular precipitation reactions, when the two water-soluble salts in an aqueous medium are mixed, the cation of one and the anion of the other would interact and form a precipitate. This precipitate will likely coalesce and accumulate at the bottom of the container because the aqueous phase provides a suitable environment for molecules to migrate and coalesce or to assemble and be transported. This accumulation of solids is called sedimentation [3]. However, when the gel medium is used, and the diffusion controls the precipitation process, particles cannot move freely as they would in aqueous media due to the compact structure of the gel medium; therefore, they cannot collect and accumulate instantaneously. So, ion mobility is also controlled by the gel medium. This is where the secret of Liesegang patterns begins to emerge gradually.

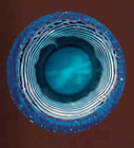
For a better understanding, the processes emerging from the pattern formation should be followed moment by moment. As an artificial one-dimensional example of Liesegang pattern formation, cobalt (II) hydroxide systems can be examined. In a real experimental procedure, cobalt (II) chloride was incorporated into the gelatin as the inner electrolyte, and an aqueous sodium hydroxide solution was prepared as the outer electrolyte in a thin test tube [9]. The concentration of the outer electrolyte, sodium hydroxide, was ten times greater than that of the inner electrolyte, cobalt chloride. Since the gel environment restricted ionic movement, the concentration of the outer S electrolyte that could diffuse into the gel was reduced, allowing the precipitation reaction to occur in a more limited space. After the diffusion started from the diffusion front, the amount of hydroxide from the outer electrolyte increased gradually in the gelatin. The first band emerged when the concentration of constituent ions reached the Ksp of cobalt(II) hydroxide, $Co(OH)_2$ accumulated in this region, resulting in the exhaustion of hydroxide ions. When the anion amount decreased, precipitation also drastically reduced, and no precipitation band appeared in that space, known as a depletion zone. No band formation was observed until the amount of hydroxide ions was replenished, which was possible by diffusion, since neither diffusion nor back-diffusion could compensate for the concentration to reach the Ksp threshold [9]. This reaction-diffusion pattern repeated itself periodically, leading to the formation of bands.

LAWS FOR PATTERN FORMATION

There are three empirical laws describing Liesegang pattern formation. These laws help characterize and demonstrate the mathematical basis of spontaneous band formation. Since band characteristics repeat themselves regularly in a sample, certain variables and laws are derived based on this dependence.

The spacing law is about the distance of the nth and (n+1)th bands from the gel-outer electrolyte interface. The distances between the positions of bands xn and xn+1 are measured from the exact point of the diffusion front [9]. Recalling the main feature of the geometric series, the ratio between the two adjacent elements should be equal and a constant function [6]. The consecutive distances satisfy that rule as follows [10]:

$$1 + p = \frac{x_{n+1}}{x_n} \quad (4)$$



Now, a new parameter appears. The ratio 1+p is called the spacing coefficient, which depends on the external and internal conditions rather than being a universal, definite number. Thankfully, scientists successfully turned it into a law with one type of function: concentration. The functional link between distance and concentration enables scientists to discover and characterize other parameters. This law, which was named after Matalon and Packter, is given below [3]:

$$p = F(b_0) + G(b_0)\frac{b_0}{a_0} (5)$$

In this context, F and G are monotonically decreasing functions of the inner electrolyte concentration, b0. a0 in the equation refers to the outer concentration, the ion is in the aqueous medium [3]. Moreover, it should be noted that the concentration of the outer electrolyte is inversely proportional to the p value when b0 is kept constant, indicating that a decrease in the outer electrolyte concentration results in higher p values and increased spacing. By the functions and equations, experimental and computational studies can be conducted.

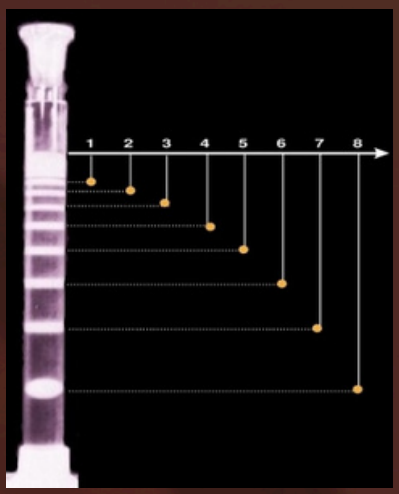


Figure 2. Geometrical representation of the spacing law [10].

The width law is another important law that states the width refers to the numerical extent of the bands. Surprisingly, band widths also follow a pattern on their own.

Now, another parameter, the quotient of the width series, is used to describe it, where wn and wn+1 are the bandwidths of the nth and (n+1)th bands, respectively [10]:

$$Q = \frac{W_{n+1}}{W_n} (6)$$

Lastly, the crucial law concerns that time dependency of the pattern formation resulting from the diffusion factor. The time law states that the time tn when the nth band is formed, and the square of the position xn is proportional to each other [3]:

$$\frac{{x_n}^2}{t} = k (7)$$

This law is derived by considering the diffusion process, where k is a constant. This relationship describes various aspects of the Liesegang patterns. Considering all the spacing, width, and time laws, the mathematical order of reaction-diffusion systems can be determined quantitatively.

FURTHER RESEARCH AND APPLICATIONS

Considering the versatility of external impacts on pattern formation, Liesegang systems are open to discovery through changes in conditions, such as concentration, gel media, and the presence of different types of ions [11]. Also, temperature has a considerable impact on the patterns [12]. Researchers try to develop new combinations and observe how they behave. Fortunately, with the development of technology, the analysis and characterization of reaction-diffusion systems have become convenient. Instruments such as scanning electron microscopy aid in investigating the macrostructures of systems and their microstructures on a small scale [2].

Through such instrumentation, research on Liesegang patterns is expected to gain interest, and new, challenging discoveries are likely to be made. Practically, Liesegang patterns can be utilized in the design of bioceramic materials. Since they are mineralized hydrogels, they can be used for bone regeneration in humans by using appropriate ions and gels [13].

The versatility of ions, precipitates, and gel combinations, combined with the sensitivity of external conditions, offers a wide range of research opportunities. This world of orderly, yet scattered patterns, has opened the doors to a different world for scientists who strive to explore it. We wish everyone interested a pleasant journey into this world.

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BLACK HOLE CHEMISTRY

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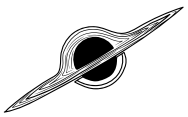
The concept of black holes began in 1783 with the Royal Society's publication of a letter by geologist John Michell written to Henry Cavendish [1]. Michell arrived with this concept when thinking about a theoretical way to calculate a star's mass. Michell agreed with Newton's notion that light is composed of tiny material particles. He argued that similar to projectiles thrown upward from the Earth, such particles bursting from a star's surface would have their speed decreased by the star's gravitational attraction. He believed it could be possible to determine a star's mass by monitoring the decrease in the speed of light from that star [2]. Michell wondered how much of an impact this may have. He was aware that for a projectile to escape from the gravitational pull of a star, it must move faster than a particular threshold speed. The star's size and mass essentially determine this "escape velocity". He asked himself: ''What would happen if the gravitational pull of a star was so great that its escape velocity was greater than the speed of light?''. Then, Michell understood that the light had to come back to the surface. Ole Roemer had discovered the estimated speed of light a century earlier, thus he knew it.

Therefore, considering an identical average density, Michell could easily determine that for a star larger than 500 times the size of the Sun, the escape velocity would be more than the speed of light. Since light cannot leave such a body, it would be undetectable to the outer world. This was Michell's concept of a "dark star," later referred to as ''black hole'' [2].

Michell was incorrect on one issue, even though he still provided the correct response. Despite the local intensity of gravity, light travels through space at a constant speed, as it is now understood thanks to Einstein's theory of relativity from 1905. Therefore, Michell's suggestion to determine a star's mass by determining the speed of light would not have been successful. However, he was right when he said that if an object's escape velocity is greater than the speed of light, it must be invisible. This idea was far in advance of current understanding of science; therefore, it didn't have a significant impact [2].

Following the publication of Einstein's theory of general relativity in 1916, the concept of black holes was rediscovered.



The equations developed by Einstein were later solved by Karl Schwarzschild for the situation of a black hole, which he conceptualized as a spherical volume of twisted space encircling an intense mass and as entirely imperceptible to the outside world. Then, research by Robert Oppenheimer and others generated the hypothesis that collapse of a large star could create such an entity. Physicist John Wheeler first used the phrase "black hole" in 1968 after finding more specifics about the characteristics of black holes [2]. Then, black holes predicted by gravitational physics contradict the principles of thermodynamics as they would need to be at absolute zero temperature because of their strong gravitational attraction preventing them from emitting anything. Hypothetically, the whole system would seem to contain less entropy if a hot object was captured by a dark star that is considered to have no temperature. The Second Law of Thermodynamics stating heat moves from hotter to cooler areas in any spontaneous process and that overall entropy of the system must rise, could be disrupted in this instance [3].

In 1972, Jakob Bekenstein identified the contradiction of the Second Law of Thermodynamics by understanding the dimensions of a black hole's event horizon, which is a limit in astrophysics beyond which no observer from the outside is able to impact by an event [4], must ultimately be related to its thermodynamic entropy [5]. A year later, Stephen Hawking introduced the concept of a black hole's temperature, and black hole thermodynamics emerged as a separate field in physics very soon [6].

Initially, Jacob Bekenstein introduced the mathematical connection between black holes and thermodynamics in 1973 when he proposed the idea of black hole entropy. Bekenstein argued that black holes must have entropy proportional to the area of the event horizon [7], and this theory claimed that black holes appear as thermodynamic systems in addition to gravitational bodies. Stephen Hawking showed that black holes emit thermal radiation, which is known as Hawking radiation, at a temperature called the Hawking temperature according to the quantum field theory [8]. Thus, these findings demonstrated that black holes can be described using the principles of classical thermodynamics.

The concept of thermodynamic pressure was neglected for a while, making black hole thermodynamics completely distinct from any thermodynamics typically used in laboratory settings. Later, the concept of vacuum pressure emerged as vacuum energy, expressed through a cosmological constant, about 40 years after black hole thermodynamics first appeared. Additional studies revealed that black holes perform similar to thermodynamic systems analysed by chemists. Subsequently, black hole thermodynamics evolved into what's known as Black Hole Chemistry over the next fifteen years thanks to the extensive research [9,10].

The classical principle of thermodynamics is connected to the physical features of black holes. It can be shown that black holes are statistically and theoretically similar to thermodynamic systems:
The Zeroth Law of Thermodynamics, which concerns thermal equilibrium, is related to black hole mechanics in how a uniform temperature beyond the event horizon is determined by constant surface gravity [11]. The First Law of Thermodynamics, emphasizing energy conservation, is related with how variations in temperature, entropy, electric charge, and angular momentum interact within black hole mechanics.

The Second Law of Thermodynamics, which concerns entropy increase, is related to how entropy grows as the area of the event horizon expands over time [7]. The Third Law of Thermodynamics, which states the impossibility of reaching absolute zero, is related to the event horizon remaining unchanged as the temperature approaches zero, which indicates the difficulty of achieving absolute zero [12]. Thus, these interactions suggest that thermodynamic factors, including energy, temperature, and entropy, can be used to describe black holes.

According to the four principles of black hole dynamics, the field of the event horizon needs to be identified with entropy and the surface gravitational field of a black hole with temperature, ideally related by proportionality constants. If black holes are regarded as completely gravitational objects, they have zero temperature and zero entropy according to the no-hair theorem [8]. Therefore, the fundamentals of black hole mechanics remain unchanged. However, it is discovered that black holes release thermal radiation which is known as Hawking emission at a temperature derived from quantum-mechanical considerations:

$$T_H = \frac{\hbar c^3}{8\pi G k_B M} (1)$$

Where, $\hbar$ is Planck constant, c is speed of light, G is Newton constant, k_B is Roltzman constant, and M is the mass of a non-rotating black hole. The equation (2) establishes the proportionality constant of the Bekenstein– Hawking entropy from the first law of black hole thermodynamics:

$$S = \frac{1}{4} \frac{k_B c^3}{G\hbar} A (2)$$

Where A is the area of the event horizon and ¼ arises from combining quantum mechanics, general relativity, and thermodynamics. Neither p,ressure nor volume was included in classical black hole thermodynamics; however, this gap was addressed through research in Anti-de Sitter (AdS) space. The cosmic constant can be considered a negative pressure in AdS space as:

$$P = -\frac{\Lambda}{8\pi} (3)$$

Where, Λ is the cosmological constant from Einstein's field equations. Consequently, the volume of a thermodynamic black hole is described as:

$$V = \left(\frac{\partial M}{\partial P} \right)_{S,Q,J} (4)$$

The equations (3) and (4) make it possible to explore black holes utilizing P-V diagrams in a manner identical to that of classical gases [13] and this method is the basis of Black Hole Chemistry as well as one of the initial steps into examining black holes as chemical systems.

Consequently, ''black stars'' and ''black holes'' are different terms and black holes perform as thermodynamic systems in addition to being mysterious cosmic objects. Today, scientists recognize that black holes possess temperature and entropy, similar to thermodynamic systems, based on Bekenstein's and Hawking's studies. Moreover, subsequent research has also revealed that black holes can exhibit pressure, volume, and even phase changes, which are identical to phase transitions in fluids. Then, Black Hole Chemistry has emerged as a distinct field as a result of these studies.

This area of study helps scientists establish connections between thermodynamics, gravitation, and quantum physics. This could ultimately lead to a deeper understanding of the cosmos as well as a reference for future studies since research in this field is still ongoing with the aim of expanding the understanding of black hole thermodynamics.

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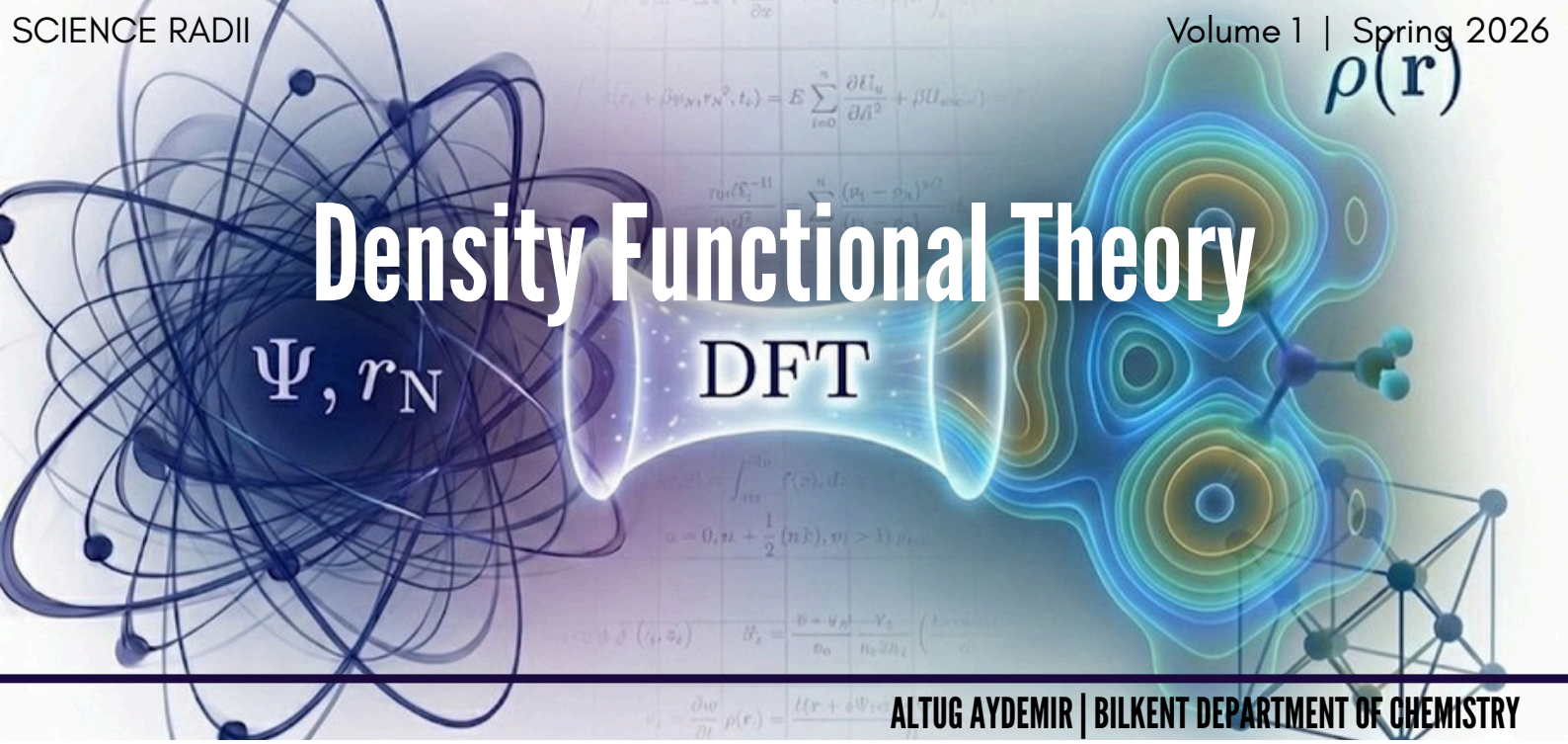

Density Functional Theory

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Density Functional Theory (DFT) is a cornerstone of modern computational chemistry and solid-state physics. In quantum mechanics, the wavefunction must be determined to obtain information about the electronic structure of the system. However, for many-particle systems, the exact wavefunction cannot be found, and an approximate wavefunction must be used. Generally, finding an approximate wavefunction is computationally expensive and time-consuming. However, DFT provides an alternative way to describe the electronic structure of the system by using electron density instead of its wavefunction[1]. This makes it significantly more efficient than Hartree-Fock and post-Hartree-Fock methods, which require solving the complex 3N-body problem (N: number of electrons) to formally reduce to a single body problem. Therefore, Hartree-Fock methods are computationally inefficient. DFT has proven itself as an accurate method that can be used to find molecular geometries, electronic band structures, etc.

From Many-Electron Wavefunctions to Electron Density

The central problem of quantum chemistry is solving the Schrödinger equation for many-electron systems:

$$H\Psi\left(r_1, r_2, \ldots, r_N\right) = E\Psi\left(r_1, r_2, \ldots, r_N\right) (1)$$

where Ψ is the many-electron wavefunction that is a function of electronic coordinates, and Hˆ is the Hamiltonian that gives the energy of the system[1]. However, this equation cannot be solved exactly, since the complexity of the equation increases quickly with the number of electrons [2], and the Coulombic interactions between the electrons prevent an exact solution from being found. [3].

So, instead of using a complicated wavefunction, can we use a physical observable to calculate the properties of a system [4]. DFT is founded on using the electron density in place of the wavefunction. As such[1]:

$$\rho\left(r\right) = N \int \left|\Psi\left(r_1, r_2, \ldots, r_N\right)\right|^2 dr_2 \ldots dr_N (2)$$

Where ρ is the electron density, which only depends on the spatial coordinates of the electrons.

$\left|\Psi\left(r_1, r_2, \ldots, r_N\right)\right|^2$ is the probability density that allows us to find the probabilities of a measurement.

When the integral given previously is evaluated, the total number of electrons in a system can be found,

$$\int \rho(r)dr = N \quad (3)$$

In DFT, the main parameter is electron density, or ρ(r), which greatly reduces the complexity and allows for the calculation of physical properties such as energy[1].

The Hohenberg-Kohn Theorems

There are two theorems that are essential for DFT, and they were developed by Pierre Hohenberg and Walter Kohn in 1964. The Hohenberg-Kohn Existence Theorem: This theorem states that the ground-state energy and the properties of the system at the ground-state are uniquely determined by the electron density [4]. Meaning that, the ground-state energy can be formulated as a functional of the ground-state electron density.

$$E[\rho] = T[\rho] + V_e[\rho] + \int \rho(r)V(r)dr \quad (4)$$

Where E(ρ) is the energy functional, $V_e[\rho]$ is the potential energy that comes from electron-electron repulsion, and ∫ρ(r)v(r)dr is the external potential energy term [1]. The Hohenberg-Kohn Variational Theorem: This theorem states that there is a true ground-state energy functional and a corresponding electron density, where the value of the energy functional with a trial density function cannot be lower than the true ground-state energy functional [5].

$$E_O = min_\rho E[\rho] \quad (5)$$

: and,

$$E[\rho] = F[\rho] + \int \rho(r)V(r)dr \quad (6)$$

Where F [ρ] is the functional that includes both kinetic and electron-electron interaction energies [1].

Moreover, the variations in the ground-state electron density subjected to the constraint [1,5]:

$$\delta[E[\rho] - \mu \int \rho(r)dr] \quad (7)$$

Thus, the ground-state electron density must satisfy the equation 5:

$$\mu = V(r) + \frac{\delta E[\rho]}{\delta \rho} \quad (8)$$

These theorems mathematically establish expressions for quantum mechanical energy in terms of electron densities [1]. But, they do not provide a way to find a functional that can be used to do these calculations [5]. In a way, they are only proofs of existence for an energy functional.

The Kohn-Sham Equations:

In 1965, Walter Kohn and Lu Jeu Sham formulated a method to approximate the unknown functional, F [ρ]. In their method, the interacting many-electron system was approximated by an idealized system where there is no electron-electron interaction that has the same electron density as the original system [5]. The total energy functional in the Kohn-Sham method is formulated as:

$$E[\rho] = T_S[\rho] + \int V_{ext}(r)\rho(r)dr + \frac{1}{2}\int \frac{\rho(r)p(r')}{|r-r'|}drdr' + E_{XC}[\rho] \quad (9)$$

where T [ρ] is the kinetic energy of the non-interacting particles, the second term corresponds to the external potential energy, the third term is the potential energy that comes from electron-electron interaction, and Exc[ρ] is the exchange-correlation energy functional [1]. The last term accounts for the difference between true kinetic energy and T [ρ], and quantum mechanical effects such as exchange and correlation. [6].

When the Hohenberg-Kohn Variational Theorem is applied to equation 9, and energy is minimized with respect to ρ, the Kohn-Sham equations can be derived:

$$\left[\frac{-1}{2}\nabla^2 + V_{eff}(r)\right]\psi_i(r) = \varepsilon_i\psi_i(r) \quad (10)$$

where the effective potential is given by

$$V_{eff}(r) = V_{ext}(r) + \int \frac{\rho\left(r'\right)}{|r-r'|}dr' + V_{XC} \quad (11)$$

the solutions of the KS equation give KS orbitals [1].

$$\rho(r) = \sum_{i}^{occ} |\psi_i(r)|^2 \quad (12)$$

Taking the square of KS orbitals and taking a sum over all occupied KS orbitals will give the electron density of the system[1]. Moreover, KS equations are self-consistent, and by starting from an initial guess for ρ(r), one can solve the KS equation and calculate the new density of the system according to this initial solution. Then, by using this new density, the equation can be solved iteratively until the change of density decreases below a certain threshold.

Applications of DFT:

Following the publication of these seminal works on the theoretical formulation of DFT and the development of exchange and correlation functionals, such as the BP86 functional, it gained popularity in computational chemistry and solid-state physics. In quantum chemistry, DFT can be used to predict molecular geometries, electronic charge densities, and molecular orbitals. In spectroscopy, DFT can be used to calculate vibrational frequencies of molecules, electronic excitation energies [7].

In material science, DFT can be used to calculate the band structure and density of states for materials. DFT has a crucial role in nanoscience, and it can be used to study structures such as graphene, nanotubes, and quantum dots. DFT can also be used in biochemistry and molecular biology. For example, it can be used in drug design and modeling active sites in enzymes.

Conclusion:

By reformulating the wavefunction approach to quantum mechanics by using electron densities, DFT provides an elegant, accurate, and efficient way to calculate the electronic structure of molecules or condensed-matter systems. Despite its mathematically rigorous theory, it became a workhorse for computational and theoretical chemistry.

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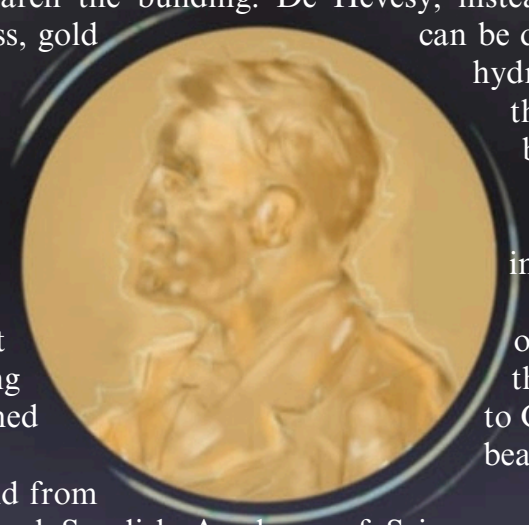
The corner of knowledge

Dissolving Nobel Medals: How Chemistry Protected Scientific Legacy

YAGMUR YAVUZ

When Germany occupied Denmark in April 1940, the Niels Bohr Institute in Copenhagen became an immediate target for Nazi searches. For years, the Institute had been a refuge for persecuted scientists, and at the time of the occupation, it held two highly sensitive objects: the Nobel Prize medals of Max von Laue (Physics, 1914) and James Franck (Physics, 1925). Both men had sent their medals to Niels Bohr for safekeeping. Von Laue opposed the Nazi regime; Franck, of Jewish descent, had resigned from his post in Germany in protest in 1933. Under Nazi law, exporting gold was prohibited, and possession of these medals in Denmark could have led to severe consequences. As German troops entered Copenhagen, Hungarian chemist George de Hevesy, then working in Bohr's laboratory, found a way to prevent the medals from being seized. Hiding them physically was risky; Bohr believed the Nazis would thoroughly search the building. De Hevesy, instead, turned to chemistry. Despite its chemical inertness, gold can be dissolved in aqua regia, a mixture of three parts hydrochloric acid to one part nitric acid. On the day of the occupation, de Hevesy placed both medals into a beaker of aqua regia. The reaction was slow, as gold is chemically inert and requires time to form soluble chloroauric acid. By the time Nazi forces inspected the Institute, the medals had fully dissolved into an orange-colored solution stored in plain sight on a laboratory shelf. The beaker went unnoticed during the search. De Hevesy fled to Sweden in 1943 but returned to Copenhagen after the end of the war. Remarkably, the beaker remained untouched. He then precipitated the gold from the solution and sent the recovered metal to the Royal Swedish Academy of Sciences around 1950. Using this original gold, the Nobel Foundation recast both medals. Laue and Franck received their newly struck medals in 1952.



This case illustrates a rare intersection of scientific expertise, ethical responsibility, and wartime necessity. By applying fundamental chemical principles under extraordinary pressure, de Hevesy preserved not only two physical artifacts but also the symbolic integrity of scientific achievement.

Structural and Functional Properties of Iron–Sulfur Cluster Assembly Proteins: A Mini Review of IscS, IscU, and CyaY

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Iron–sulfur (Fe–S) clusters are multifunctional cofactors involved in a broad variety of biological processes, including respiration, DNA repair, and redox regulation. Their formation requires a complex network of proteins, including IscS, IscU, and CyaY. This mini review gives an overview of structural and functional information on these key proteins of the Fe–S cluster assembly pathway, drawn from the literature between 2010 and 2025. We cover their roles in different cellular systems, ranging from plants to mammals, their iron and sulfur coordination, and their interaction within the global Fe–S cluster biosynthetic machinery. This short synthesis aims to present background information for students and beginning researchers with interests in mitochondrial biology, redox biochemistry, and disease mechanisms involving Fe–S proteins.

Introduction

Fe–S clusters are evolutionary cofactors composed of iron and inorganic sulfur, generally in the form of [2Fe-2S] or [4Fe-4S] clusters. They are involved in electron transport, enzyme function, and regulation. Assembly of clusters is carried out by highly characterized protein machineries, the ISC (iron–sulfur cluster), SUF (sulfur mobilization), and CIA (cytosolic iron– sulfur protein assembly) pathways. Mitochondrial ISC machinery initiates the process in eukaryotes, while CIA regulates cytosolic and nuclear maturation of Fe–S proteins [1].

The ISC pathway of mitochondria and bacteria includes IscS (a cysteine desulfurase), IscU (a scaffold protein), and CyaY (a frataxin homolog). IscS catalyzes activation of sulfur from cysteine to produce an intermediate persulfide that is delivered to IscU, in which it loads iron to give nascent Fe–S clusters. These are subsequently delivered to recipient apoproteins by chaperone systems [2].

The SUF machinery, both in plant and bacterial plastids, is oxidative-stress resistant and uses a unique scaffold (SufBCD complex) to possess a flavin redox cofactor important for the stabilization of sulfur intermediates and oxidative environment resistance [3].

Plant systems are more complex since ISC and SUF pathways are located within chloroplasts and mitochondria, respectively. These pathways employ different but functionally homologous proteins, which allow specialized metabolic processes and stress responses [4].

Interestingly, Fe–S cluster assembly occurs in two broad phases: one is de novo cluster assembly on scaffold proteins like IscU, and the other is transfer and insertion of preassembled clusters into recipient apoproteins. Both phases are tightly regulated and evolutionarily conserved [5]. The CIA pathway, indirectly not being regulated with IscS or IscU, is dependent on ISC- derived precursors and helps in the Fe–S cluster incorporation into nuclear and cytosolic proteins in general cellular metabolism [6]. Familiarity with these pathways provokes a basis upon which to deconvolute the physiological and biochemical function of Fe–S clusters in a variety of biological contexts. These things are very important in cellular metabolism. It can be seen by their conservation through species and evolution.

Structural Features of IscS, IscU, and CyaY

IscS is a cysteine desulfurase that transfers sulfur into clusters when being assembled. IscS prefers to exist as a homodimer and bears the cofactor pyridoxal phosphate (PLP). IscU is a kinetic scaffold on which initial cluster assembly takes place. CyaY is a frataxin structural homolog with the best capacity to bind iron and to modulate iron availability when a cluster assembles. Structural analysis shows how these proteins interact transiently to enable effective iron and sulfur transfer [5]. Sulfur transfer and cysteine are attached by the active site of IscS, while conformational change in IscU is enabled to stabilize intermediate clusters. CyaY has a conserved β-sheet structure and negatively charged surface regions suitable for iron coordination. The SufBCD complex, despite being a member of the Isc system, has given structural insights into alternative scaffolds and shown the function of flavin redox cofactors in Fe–S assembly with functional similarity to the IscU function [3].

Functional Roles in Fe–S Cluster Biogenesis

IscS catalyzes cysteine-to-alanine conversion through a persulfide sulfur intermediate that is passed on to IscU. The reaction is strictly regulated because an excess or lack of Fe– S clusters can cause oxidative stress or metabolic inhibition [1]. Isc machinery functions in a linear manner with assembly and targeting to acceptor proteins being extremely faithful. Intermediates must be strongly regulated to avoid cytotoxicity due to free iron or aberrant cluster assembly. In plant organisms, functional diversification of Fe–S cluster proteins like orthologs of IscU and IscS indicates plastid and mitochondrial compartment adaptation. The proteins are involved in redox balance and help in photosynthesis and respiration [4]. Coordination between nuclear-encoded and organelle-targeted proteins also illustrates the complexity of Fe–S assembly in multicellular organisms, where complex regulation is required to coordinate developmental and environmental cues.

Protein–Protein Interactions and Regulatory Mechanisms

IscS, IscU, and CyaY are a transient complex whose stability is controlled by the availability of cellular iron. Frataxin (bacterial CyaY) can act as an iron donor or regulatory inhibitor depending on redox and iron status. Coordination among these proteins avoids free iron toxicity and ensures correct cluster transfer [7]. For example, regulation of iron loading on IscU by frataxin is dependent on binding to IscS and regulating the overall rate of cluster biosynthesis.

Fe–S cluster reactivity with reactive molecules like oxygen and nitric oxide reveals both their potential to serve as regulators and their sensitivity. Reactivity also indicates the necessity of having a particular cluster assembly in order to prevent unwanted oxidative reactions [8]. Through feedback control mechanisms, iron sensors and redox-sensitive transcription factors play an important role in regulating Fe–S cluster homeostasis under a variety of biological circumstances.

Fe–S Clusters in Cellular Processes and Disease

Apart from electron transport, Fe–S clusters also play a role in enzyme catalysis and DNA metabolism. Cluster biosynthesis and iron homeostasis can be stopped by frataxin loss. This causes defects in cluster assembly which can lead to mitochondria to malfunction and have disorders [9].

In mammalian cells, carrying the cluster from IscU to recipient protein is done by specialized systems. If there is a defect in these processes, cellular metabolism and viability can be affected by it [2].

Recent findings reveal the role of new assembly factors in cluster maturation and transport in mammalian cells, including GLRX5 and HSC20. This helps us better understand the molecular handoff processes in the clusters within mammalian cells [6].

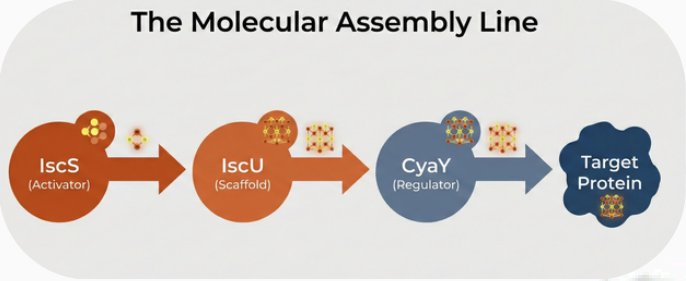
The role of Fe–S clusters in disease has also been explored for neurodegenerative and metabolic diseases. If clusters are defective, these can cause iron to not be distributed correctly and therefore increase oxidative damage [10].

Emerging Research and Perspectives

Recent evidence shows that [4Fe–4S] cluster assembly needs specialized complexes in mitochondria that include scaffold, transfer, and regulatory components [11]. Besides, the connection between genome stability and cluster assembly has been established by evidence of Fe–S cluster requirements in polymerases and DNA repair proteins. For example

MMS19 has been described as a protein that connects cytosolic Fe–S cluster assembly and DNA metabolism and impacts genome integrity [12]. Furthermore, studies have indicated that the formation of active eukaryotic DNA polymerase complexes is dependent on the incorporation of an Fe–S cluster, which is required for their catalytic function [13]. Furthermore, defects in Fe–S cluster biogenesis have also been implicated in Friedreich's ataxia pathogenesis, a neurodegenerative disease characterized by iron overload, oxidative stress, and mitochondrial dysfunction [14]. These findings as a whole show the ubiquitous role of Fe–S clusters in functions outside of their established metabolic roles and propose their involvement in cell homeostasis and resistance to genetic instability.

Finally, novel roles for Fe–S cluster function in vascular biology have been discovered with regulatory roles in oxygen sensing and redox signaling, adding further to their biological significance [15].



Conclusion

Assembly of Fe–S clusters depend on IscS, IscU, and CyaY, which together enable the correct synthesis, delivery, and regulation of these critical cofactors. Further research on these clusters is required to completely understand their interactions, dynamics, and disease significance. This background is necessary to fully understand the general significance of Fe–S clusters in cellular life and human disease.

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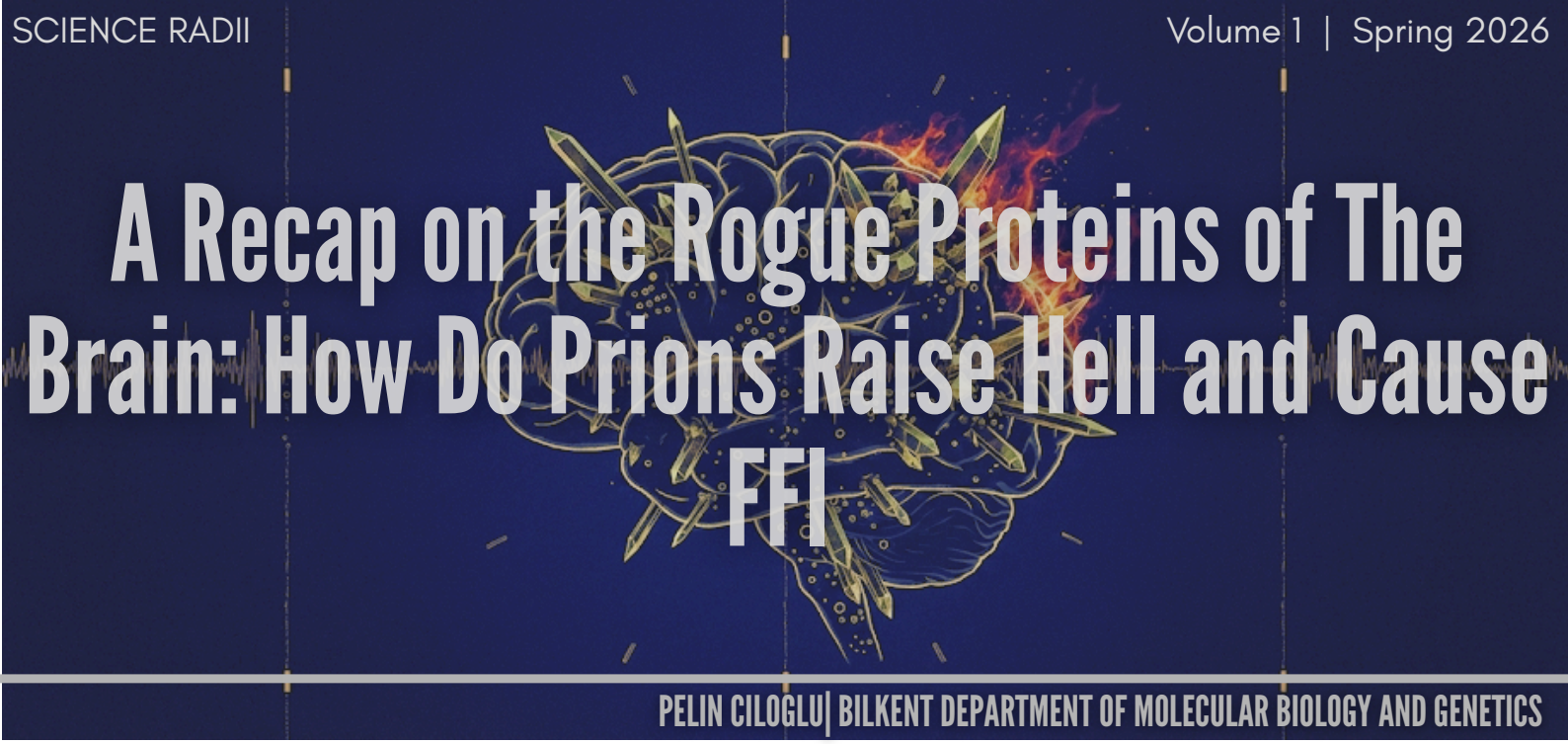

A Recap on the Rogue Proteins of The Brain: How Do Prions Raise Hell and Cause FFI

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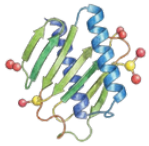
Halloween season is officially over, and yet FFI, which is familial fatal insomnia, is here to petrify any hypochondriac for good. FFI, formerly known as thalamic dementia, is an autosomal dominant disease that is caused by a mutation in the PRNP gene, which is responsible for prion proteins [1]. Prion diseases are also known as transmissible spongiform encephalopathies, or TSEs, and they can be heritable, transmissible, or even sporadic. Moreover, heritable prion diseases are only 10% of the known TSEs, and 1 to 1.5 per million in a population usually report having hereditary or non-hereditary prion diseases [2]. However, certain TSEs can be more prevalent in certain regions of the world, like how kuru disease, another example of a possibly terrifying TSE, was more common in Papua New Guinea in the twentieth century in certain tribes that performed ritualistic cannibalism and contracted infectious prions [3]. TSEs are known for causing medical abnormalities, such as cognitive impairment and the formation of amyloid plaques [4]. The accumulation of plaques usually leads to cellular death, especially in neurons, through vacuole formation, which is why prion diseases are considered lethal [4]. Some prion diseases affect neurons in the central nervous system, whereas some can also affect certain peripheral tissues such as the lymphoid system prior to the propagation of prions in the brain [5]. Recent theories tie vacuolation with prions and propose that the abnormalities in prion function disrupt regular cell membrane functions and form channels that comprise integrity [6]. Vacuoles are membrane-bound lysosome-like organelles that are commonly found in plant cells [7]. However, animal and human cells also do have vacuole-like vesicles that perform the task of disposing of harmful toxins. Moreover, some recent studies have shown that vacuoles can, in fact, begin to form in human cells in vivo after the introduction of bacterial or viral pathogens and various compounds [8]. Cytoplasmic vacuolation is triggered by external stimuli and is a morphological phenomenon that can occur when cytotoxic stimuli exist in the cell [8].

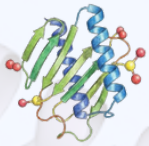
When regular prions, PrPC, aggregate and misfold, they turn into pathogenic proteins, PrPSc. Furthermore, PrPC and PrPSc have different secondary and tertiary tructures, and even though they contain different amounts of beta sheet and alpha-



helical contents, they usually have the same amino acid sequence, which depends on the type of mutation and the disease [1]. Nevertheless, the PrPSc isoform, due to its higher beta sheet content, can be resistant towards degradation and proteinase K, and can be insoluble even in detergent. In the case of FFI, the disease is caused by a 2 single-point highly penetrating mutation where aspartic acid is replaced with asparagine at D178N of the PRNP gene, which is in codon 178 [9]. FFI is highly penetrating due to the visible phenotypical effects of the mutation and therefore the disorder. Nonetheless, since there are many subcategories of prion diseases, another mutation needs to accompany the D178N mutation for FFI, which is the M129V PRNP polymorphism. In this case, the D178 mutation is linked to the methionine of the M129V polymorphism. For instance, if the polymorphism on codon 129 is in valine, the disease is called genetic Creutzfeldt-Jakob Disease (CJD), and it is another example of a TSE [1]. Ergo, polymorphisms can make individuals more susceptible to prion diseases as mutations in the PRNP gene can lead to decreased resistance towards PrPSc formation [10]. Moreover, PrPScs, the abnormal proteins, can recruit PrPC proteins to convert more normally functioning prions into pathogenic prions, which is how prions propagate in the brain [9].

The common clinical characterization of FFI is as follows: insomnia that progresses and worsens over time, which leads to changes in the circadian rhythm, cognitive impairment, and altered hormone secretion [11]. The generally accepted onset for FFI is considered to be between 40 and 60 years, and due to the lethality of the disease, the disease lasts for 7 to 18 months [11]. The thalamus, especially the anteroventral and dorsomedial regions of the thalamic nuclei, is affected by neuron loss and gliosis, which leads to a disrupted circadian rhythm and a disrupted endocrinesystem [11]. At the early stages of the disease, the patients proved to show abnormalities in slow-wave and rapid-eye movement phases in their sleep cycle, and their insomnia progressed over time [12]. FFI has 4 stages. In the first stage of FFI, patients report onset insomnia that worsens over time followed by panic attacks and paranoia. Some patients can claim instances of lucid dreaming [2]. However, patients at the initial stages of FFI usually had minimal memory or attention impairments, even though, through the course of the disease, such deficiencies progressed [12]. As FFI progresses, people with FFI can have hallucinations, and in the last stages of the disease, they can enter coma and stupor, which are different stages of unconsciousness. The third stage of FFI includes total insomnia and complete disruption of the biological clock. Furthermore, FFI patients can have dysautonomia, which can induce hypertension, hyperthermia, and tachycardia. Moreover, difficulty in speaking and ataxia, which is poor muscle control, can be observed in patients [12]. Personality changes and mental health problems such as depression, anxiety, and specific delusions, along with weight loss and involuntary movements, are also some clinical features that are looked for to diagnose FFI [2]. The fourth and final stage of FFI is defined by the patients' inability to talk or move, the eventual comatose phase, and lastly death [2]. Additionally, since methods like MRI and CT are inadequate to fully diagnose FFI, genetic testing and polysomnography, which can a show reduction in overall sleep when utilized [2].

Lastly, since the research about prion diseases is still ongoing, it is evident that there is still a lot to discover about FFI. However, due to the delicate nature of how the disease affects individuals and their families, more people, especially in developing countries, should be aware of prion diseases, and clinicians should offer more genetic testing and care for families who have to experience the horror that is FFI.



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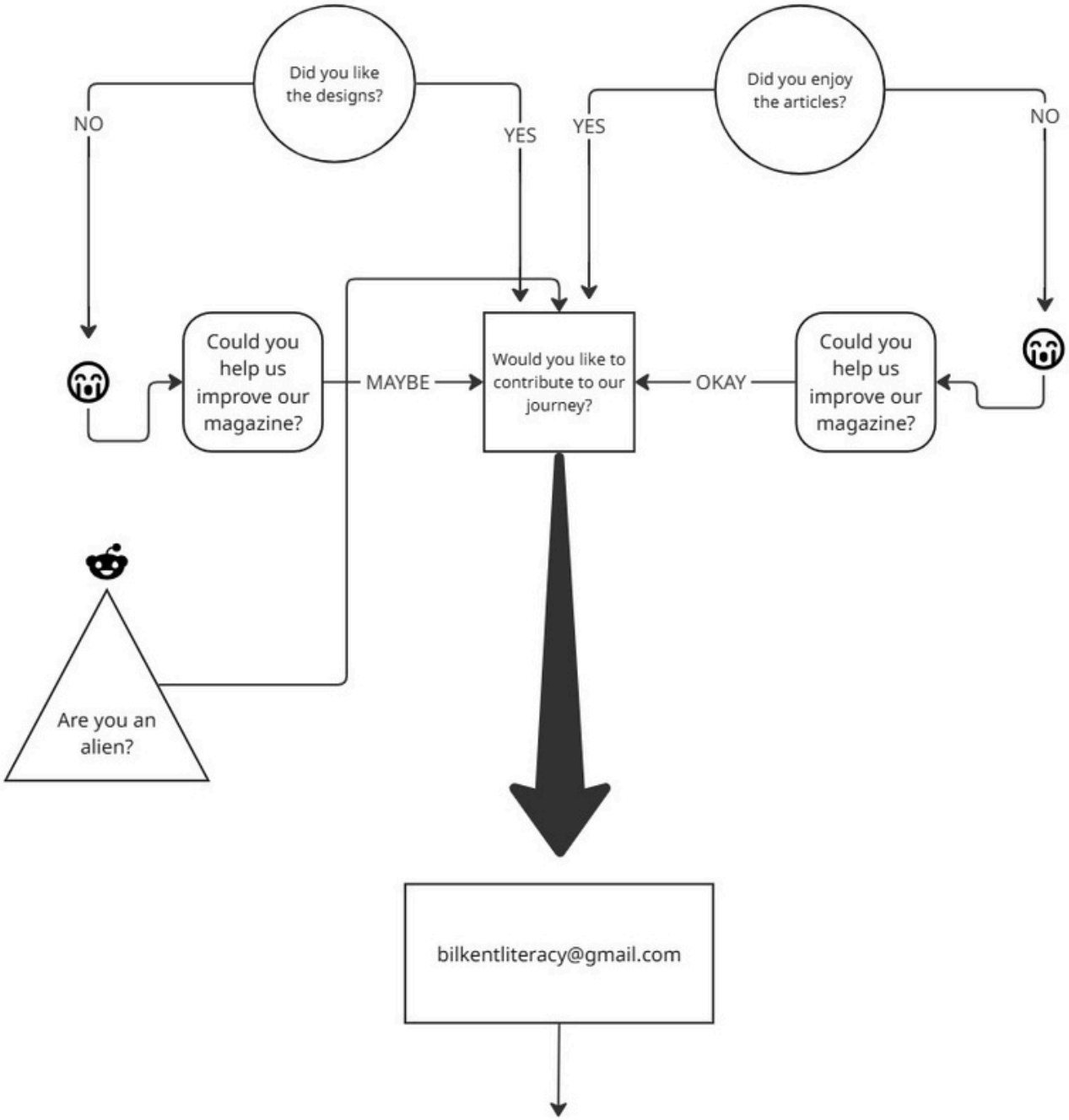

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