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3D Printing and Tissue Scaffolds for Periodontal Regeneration:A Comprehensive Review

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Abstract: ***The advancement of 3D-printed scaffolds has revolutionized periodontal regeneration by offering patient-specific solutions that enhance bone formation and tissue integration. Various biomaterials, including tricalcium phosphate (TCP), hydroxyapatite (HA), polycaprolactone (PCL), and titanium-based composites, have been explored for their biocompatibility and osteogenic potential. Strategies such as growth factor incorporation, hydrogel-based scaffolds, and guided bone regeneration (GBR) membranes have shown promising results in enhancing cellular response and mechanical stability. Custom-designed scaffolds, fabricated using medical imaging and CAD-based workflows, provide superior structural adaptation to periodontal defects, promoting vascularization and periodontal ligament alignment.***

Despite significant progress, challenges remain in optimizing scaffold degradation, enhancing mechanical properties, and ensuring long-term biocompatibility. Emerging bioprinting technologies, incorporating periodontal ligament cells and bioactive hydrogels, are being investigated to further improve tissue regeneration outcomes. Future research will focus on refining biomaterial compositions and scaffold architectures to enhance the efficacy of periodontal regeneration.

Keywords: 3D-Printed Scaffolds, Periodontal Regeneration, Bioprinting, Guided Bone Regeneration, Biomaterials

I. INTRODUCTION

Periodontal disease is a progressive inflammatory condition that leads to the degradation of the periodontium, which comprises the gingiva, periodontal ligament, cementum, and alveolar bone. Conventional treatments primarily focus on controlling disease progression rather than promoting complete tissue regeneration. However, advancements in tissue engineering and 3D printing technologies have revolutionized periodontal repair by offering innovative solutions for regenerating damaged tissues.[1]

The integration of 3D printing with biomaterial scaffolds has significantly enhanced the precision and efficacy of periodontal treatments. These scaffolds function as three-dimensional templates that closely mimic the natural extracellular matrix, providing structural support for cell attachment, proliferation, and differentiation.[2] Recent developments in scaffold technology have transitioned from monophasic to multiphasic and bioactive scaffold systems, aiming for holistic periodontal tissue regeneration rather than mere healing.[3]

The application of 3D printing in periodontal repair enables the fabrication of patient-specific scaffolds with precise structural and mechanical properties, enhancing treatment planning and procedural accuracy in bone augmentation and implant placement. The ability of 3D printing to rapidly and accurately reconstruct damaged tissues addresses limitations associated with traditional scaffold fabrication methods.

Advanced scaffold designs, such as biphasic constructs like the FGF2-PLGA/PLGA-nHA-BMP9 scaffold, facilitate the controlled and sequential release of bioactive molecules, promoting efficient cell signaling pathways and improving tissue regeneration outcomes. Additionally, the incorporation of nanosphere technology in scaffold design has further optimized the biomechanical properties and biocompatibility of these constructs by modulating the controlled release of growth factors.[4]

This review explores the principles underlying 3D printing in periodontal applications, examines the latest advancements in scaffold design, and evaluates their potential in revolutionizing periodontal regeneration.

II. FROM PROTOTYPE TO PERIODONTIUM: THE POWER OF 3D PRINTING

3D printing, also referred to as additive manufacturing or rapid prototyping, is a manufacturing process that constructs objects by sequentially adding layers to form a final product. The origins of 3D printing date back to 1986 when Charles W. Hull and Raymond S. Freed pioneered the technology, leading to the establishment of DTM Corporation in 1987 to commercialize selective laser sintering (SLS).[5]

The first commercialized 3D printing system, known as the stereolithography apparatus, was introduced in 1988, followed by the founding of Stratasys Inc. in 1989, which played a crucial role in developing fused deposition modeling (FDM). Inkjet-based printing technology further advanced in 1993, marking significant progress in the field.

III. TYPES OF 3D PRINTING TECHNOLOGIES

3D printing technologies can be broadly categorized into several types, each with distinct characteristics and applications in various industries, including regenerative medicine and dentistry.[6,7]

1) Inkjet Printing: Inkjet printing uses acoustic, thermal, or electromagnetic forces to dispense biological fluids through an orifice. This technique creates multilayered structures by selectively depositing these fluids. Inkjet-based 3D printing is particularly advantageous for building intricate biological models, as it allows for precise deposition of fluids in a controlled pattern.
2) ExtrusionPrinting: Extrusion printing is a pressure-driven process that uses pneumatic or mechanical pressure to deposit biomaterials in a continuous stream. This method is widely employed for fabricating scaffolds, where the material is extruded through a nozzle and laid down layer by layer to form a three-dimensional structure.
3) Fused Deposition Modeling (FDM): FDM is one of the most common methods used in 3D printing. It involves the extrusion of thermoplastic materials, which are heated and deposited layer by layer to build an object. FDM is especially popular in regenerative medicine due to its ease of use and ability to produce highly accurate and robust scaffolds for tissue engineering.
4) Light-Assisted Printing: Light-assisted printing includes stereolithography (SLA) and direct light processing (DLP), where a laser or optical light is used to polymerize material, forming intricate 3D structures. This technique is particularly useful for producing high-resolution and complex shapes, and it has applications in dental and tissue engineering.
5) Electrospinning: Electrospinning is a method where polymer solutions are subjected to an electric field, causing them to form fibers that are deposited in a highly controlled manner. This method is highly utilized for scaffold fabrication, particularly in regenerative dentistry, as it mimics the natural extracellular matrix structure and provides a scaffold conducive to cell growth.
6) Direct vs. Indirect 3D Printing Methods : 3D printing techniques are further classified into direct and indirect methods, each offering unique benefits in creating personalized scaffolds.
7) Direct 3D Printing: Direct 3D printing involves the direct deposition of cells, extracellular matrix, and bioactive molecules, which allows for the creation of functionalized scaffolds that are ready for tissue integration. This method offers the advantage of incorporating live cells and biologically active materials, which can promote cell signaling and enhance tissue regeneration.
8) Indirect 3D Printing:Indirect 3D printingfollows a two-step process where a mold (typically made of wax) is first printed, and then the final scaffold is cast using polymer materials. This method is often used in patient-specific applications, as it allows for customization based on the individual patient's needs, particularly in complex anatomical regions like the periodontium.

IV. 3D PRINTING WITH LIVE CELLS FOR REGENERATIVE APPLICATIONS

The integration of live cells into 3D printed scaffolds is an emerging area of research in regenerative medicine. By incorporating cellular components into scaffolds, 3D printing can promote cell-to-cell signaling, mimicking natural tissue environments and accelerating the formation of functional tissue structures. This technique holds great promise for periodontal regeneration, as it enables the creation of scaffolds that not only support cell attachment but also encourage cellular differentiation and tissue formation.

V. ROLE OF 3D SCAFFOLD DESIGN IN PERIODONTAL REGENERATION

In periodontal regeneration, 3D scaffolds design plays a critical role in mimicking the complex structure and function of periodontal tissues. The scaffolds must not only provide structural support but also promote cellular behavior in a way that mimics the natural tissue. Effective scaffold design incorporates factors such as porosity, mechanical strength, and the ability to facilitate cell migration and differentiation.

VI. MATERIALS FOR PERIODONTAL SCAFFOLD FABRICATION

A variety of materials are used in the fabrication of 3D printed scaffolds for periodontal regeneration. These materials include both synthetic polymers and ceramic biomaterials, each offering specific advantages. **Polycaprolactone (PCL) and Calcium Phosphate (CaP) :**Polycaprolactone (PCL) is a biodegradable and biocompatible polymer commonly used in scaffold fabrication.

When combined with calcium phosphate (CaP) or bioactive glasses, PCL scaffolds promote osteoconductivity and periodontal tissue regeneration. The combination of these materials enhances the mechanical properties and bioactivity of the scaffold, making it suitable for periodontal applications.

Bioactive Glasses and Other Biomaterials:Bioactive glasses have been explored as a material for scaffolds due to their ability to bond with both bone and soft tissues. These materials encourage the formation of new bone and stimulate tissue healing, which is crucial in periodontal regeneration. Other biomaterials, such as collagen and chitosan, have also been investigated for their role in scaffold design, given their excellent biocompatibility and support for cellular attachment and growth.

In periodontal regeneration, 3D scaffolds design plays a crucial role in mimicking the complex architecture of periodontal tissues. Ceramic biomaterials and synthetic polymers, such as polycaprolactone (PCL) blended with calcium phosphate (CaP) or bioactive glasses, are commonly employed for scaffold fabrication. These advancements in 3D printing and scaffold engineering hold significant promise for the future of periodontal regeneration, enabling the development of personalized and effective treatment solutions.[8]

VII. COMPARISON OF 3D BIOPRINTING TECHNIQUES: ADVANTAGES, LIMITATIONS, AND APPLICATIONS

Technique	Advantages	Disadvantages	Applications
Droplet-Based Printing	High precision, low cost, suitable for biological inks	Nozzle clogging, limited to low-viscosity materials	Bioprinting of cells, tissue engineering
Inkjet Printing	Fast, scalable, cost-effective	High pressure may affect cell viability, nozzle clogging	Bioprinting, drug delivery, tissue engineering
Electrohydrodynamic Jetting	High-resolution printing, handles high viscosity bioinks	Requires high voltage, potential cell damage	High-cell-density bioprinting, precise droplet control
Laser-Assisted Printing	No nozzle clogging, high resolution, biocompatible	High cost, complex setup	Printing high-viscosity biomaterials, cell-based applications
Stereolithography (SLA)	High accuracy, smooth surface finish	Limited to photopolymer materials, slow process	Tissue scaffolds, dental applications, medical devices
Digital Light Processing (DLP)	Faster than SLA, good resolution	Less precise than SLA, limited material choices	Medical modeling, prosthetics, tissue engineering
Selective Laser Sintering (SLS)	No need for support structures, strong printed parts	High-energy laser required, expensive setup	Bone scaffolds, prosthetics, implants
Fused Deposition Modeling (FDM)	Low cost, high-speed printing	Low resolution, poor surface finish	Scaffold fabrication, medical modeling, implants

Melt Electrowriting (MEW)	High precision, nanoscale fibers, collagen-mimicking	Complex process, requires high voltage	Periodontal scaffolds, tissue regeneration
Non-Thermal Extrusion Printing	Supports cell viability, bioink flexibility	Material properties must be carefully optimized	Cell-laden scaffolds, regenerative medicine

VIII. PERIODONTAL SCAFFOLDS: ANTIMICROBIAL AND ANTI-INFLAMMATORY EFFECTS IN REGENERATION

Scaffolds serve as a platform for cell adhesion, tissue ingrowth, and structural support in tissue engineering. In guided tissue regeneration (GTR), degradable or non-degradable membranes limit epithelial growth, allowing for gradual (4–6 weeks) periodontal connective tissue and periodontal ligament (PDL) repair. However, prolonged periodontitis may reduce the efficacy of GTR by impairing the healing capacity of PDL cells, weakening the host immune response, or excessively degrading the cellular matrix (CM).

Ideally, scaffolds should be biocompatible, easy to adapt and place, maintain space, provide clot stability, promote tissue integration, and encourage cellular proliferation. [9]Based on their origin, scaffolds are categorized as allogenic, xenogeneic, alloplastic, or as living structures when they contain viable cells. These scaffolds aid periodontal tissue regeneration by facilitating cell migration into defects. Bioactive cues such as growth factors (GFs) and cytokines enhance tissue ingrowth; however, there is limited evidence that scaffold-mediated repair is as rapid or effective as traditional GTR.

Research on biodegradable scaffolds has demonstrated significant potential. For instance, electrospun multiphasic scaffolds made from polycaprolactone (PCL), collagen type I (COL-I), and recombinant human cementum protein 1 (rhCEMP1)/amorphous calcium phosphate (ACP) have promoted CM-like structure formation in rat calvarium models.[10] Tri-phasic scaffolds incorporating spatially controlled bioactive signals and dental progenitor cells have successfully induced multi-tissue periodontium formation in animal models. Similarly, some 3D-printed tri-phasic scaffolds with distinct microarchitectures have shown promise in promoting periodontal regeneration through periodontal ligament stem cells (PDLSCs). Advances in micro-precise scaffold construction continue to contribute to enhanced structural and bioactive support.

Despite these innovations, bacterial reinfection—primarily from pathogens such as *Porphyromonasgingivalis*, *Tannerella forsythia*, and *Treponema denticola*—remains a major challenge in periodontal therapy. Even after initial plaque and calculus removal, the risk of secondary infection persists. GTR membranes hinder epithelial and connective tissue ingrowth but also obstruct blood flow, which can lead to gingival soft tissue recession and membrane exposure. This increases the risk of reinfection, especially with non-biodegradable expanded polytetrafluoroethylene (e-PTFE) membranes.[11]

Natural biomaterials such as collagen and chitosan offer excellent biocompatibility, low toxicity, and minimal immune response, making them preferred choices for periodontal scaffolds. For example, a 3D collagen scaffold with aligned 50–100 μm pores facilitated rapid PDL migration, while BMP-2-infused collagen hydrogels significantly enhanced PDL formation and attachment. Additionally, fibroblast growth factor-2 (FGF-2)-infused collagen sheets prevented epithelial downgrowth and promoted periodontal regeneration in rat models.Conventional periodontal treatment typically involves the removal of plaque, calculus, and inflammatory granulation tissue. However, managing inflammation remains crucial—particularly to mitigate potential foreign body reactions to scaffolds. Improper surgical handling or compromised systemic health may trigger inflammation, further impairing tissue regeneration.[12] Studies have shown that chitosan-based scaffolds loaded with prolonged-release meloxicam or aspirin effectively reduce post-treatment inflammation. PCL scaffolds incorporating ibuprofen have demonstrated similar anti-inflammatory benefits. Furthermore, 3D PCL scaffolds combined with tannic acid—a potent antioxidant and anti-inflammatory agent—successfully inhibited lipopolysaccharide-induced inflammation. However, most earlier applications of anti-inflammatory biomaterials were directed toward GTR membranes rather than scaffolds specifically engineered for direct periodontal regeneration.[13]

IX. 3D SCAFFOLD DESIGN AND FABRICATION FOR PERIODONTAL REGENERATION

The design of scaffolds that closely mimic the intricate structure of periodontal tissues remains a major challenge in regenerative therapy. Ceramic biomaterials and synthetic polymers play a critical role in this domain, with polycaprolactone (PCL) commonly blended with ceramics such as calcium phosphate (CaP) or bioactive glasses to support regeneration.

Ideal scaffold characteristics include biocompatibility, biodegradability, appropriate porosity to facilitate nutrient diffusion, sufficient mechanical strength, and the ability to promote proper periodontal ligament (PDL) fiber orientation and attachment.

Scaffolds are classified based on their structural complexity into monophasic, biphasic, or triphasic forms:

- Monophasic scaffolds consist of a single compartment and can be loaded with growth factors such as SDF-1 and BMP-7. For instance, Kim et al. (2010)[14] demonstrated that anatomically shaped monophasic scaffolds facilitated effective periodontal regeneration.
- Biphasic scaffolds feature distinct compartments for PDL and bone, enabling more controlled and targeted tissue regeneration. Studies by Park et al. (2018)[15] emphasized the advantage of this approach, especially when combined with cell sheet technology to improve mechanical stability and extracellular matrix deposition.
- Triphasic scaffolds go a step further by including separate compartments for cementum, PDL, and alveolar bone. These allow for more precise biomolecule delivery but present greater challenges in terms of adapting to the complex architecture of periodontal structures.[16]

The fabrication of 3D scaffolds follows a systematic process. It begins with the acquisition of periodontal defect data using CT or CBCT imaging. This data is then converted into a stereolithography (STL) file format, which serves as the basis for scaffold design. The scaffold is fabricated layer-by-layer using a suitable 3D printing technology, chosen based on the material properties and application requirements.[17]

Post-processing steps—such as support removal, sandblasting, and heat treatments—are employed to enhance the scaffold's mechanical and biological properties before clinical use. The continuous refinement of scaffold fabrication techniques, combined with emerging biomaterials and bioactive molecule integrations, holds great promise for the future of personalized and effective periodontal regeneration.

X. BIOMATRICES AS SCAFFOLDS FOR PERIODONTAL REGENERATION

Matrixes for the delivery of bioactive components have become a crucial aspect of periodontal regeneration. They incorporate biologically active substances such as bone morphogenetic proteins (BMP), enamel matrix derivatives (EMD), and growth factors (GFs). The controlled release and protection of these biomolecules during the repair process are vital. One of the simplest production methods involves surface attachment of these biomolecules to biomatrices, allowing for rapid release and direct cell activation.

The advent of 3D printing has further revolutionized the use of biomatrices in bone transplantation by enabling precise customization of scaffolds. This is achieved using computed tomography (CT) scan images and computer-aided design (CAD). These 3D-printed structures, primarily composed of polycaprolactone (PCL), offer controlled physico-chemical properties that enhance space preservation, tissue infiltration, and cell homing.[18]

Multiphasic 3D-printed matrices incorporating hydroxyapatite (HA) and PCL have been designed with microchannel compartments specific to dentin cement, periodontal ligament, and alveolar bone. These scaffolds have achieved successful periodontal tissue integration upon implantation.

The use of fused deposition modeling (FDM) has enabled the development of biphasic porous biomaterials that simultaneously support osteoblast and periodontal ligament cell proliferation. In these constructs, tricalcium phosphate (TCP) serves as the bone component, while PCL microfibrous membranes form the periodontal component. When combined with osteoconductive calcium phosphate (CP) membranes and cell sheet technology, these 3D-printed biphasic scaffolds have demonstrated efficacy in promoting alveolar bone formation and periodontal attachment in ectopic models.

The spatial orientation of periodontal ligaments plays a key role in distributing masticatory forces. With the help of 3D printing, biomaterials can now be fabricated to mimic periodontal ligament structure, thereby facilitating dental root attachment and guiding the orientation of connective tissue fibers.[19]

These advancements have led to successful outcomes in bone regeneration, periodontal ligament formation, cementogenesis, and restoration of the functional periodontal complex. Furthermore, additive manufacturing using PCL–PGA (polyglycolic acid) copolymer-based scaffolds with perpendicular microchannels has been explored to guide periodontal ligament orientation and ensure in vivo functional regeneration of periodontal tissues. [20]

XI. RESEARCH ON 3D PRINTED SCAFFOLDS FOR PERIODONTAL APPLICATIONS

Study	Scaffold Composition & Fabrication	Model & Outcome
Carrel et al.[21]	β-TCP & HA, extrusion-printed (OsteoFlux®)	Sheep calvarial defects; initial bone growth observed, but no difference after 4 months.
Extrusion Mesh Scaffold	30% HA, 60% β-TCP, 10% α-TCP, macroporosity 60%	Sheep sinus; peripheral bone remodeling in 45 days, lamellar bone in 90 days, but incomplete defect filling.
Hydrogel-based scaffolds	Electrospinning with cellular loading	Limited by cell source and culture conditions.
Cho et al.[22]	PCL scaffold with PLGA microspheres (BMP-2, BMP-7, CTGF)	In vitro on human tooth roots; improved dentin recovery, BMP-2/7 formed thicker tissues, CTGF/BMP-7 enhanced integration.
Shim et al.[23]	3D-printed PCL, β-TCP membranes vs. collagen membranes	Beagle dogs, alveolar defects; PCL/β-TCP outperformed others in biocompatibility and bone regeneration.
Dubey et al.[24]	PCL mesh (MEW) + AMP hydrogel	GBR membrane; delayed hydrogel degradation, prevented soft tissue invasion, improved bone progenitor cell support.
Hsieh et al.[25]	PDL cell spheroids on chitosan/PVA in 3D-printed PLA scaffold (FDM)	Higher alkaline phosphatase activity & mineralized matrix deposition.
Bai et al.[26]	CAD-designed Ti-Mesh, sintering additive manufacturing	0.4 mm thick mesh strong with minimal irritation; 3–5 mm pore size reduced mechanical strength.
Ti-Nb Porous Scaffold	SLM Ti-Nb alloy mesh coated with CS/G/Dox (EPD & lyophilization)	Maintained space, prevented fibroblast growth, antibacterial properties.
Dual-compartment Scaffold	Bone (BMP-7 PDL cells) + ligament (stacked cylinders with PDL cells), extrusion & casting	Ligament/bone-like structures, but poor in vivo fiber orientation control.

Vaquette et al.[27]	Biphasic scaffold (β-TCP FDM for bone, electrospun ligament compartment)	In vitro osteoblast mineralization; in vivo bone, ligament, and cement regeneration, but non-functional fiber alignment.
Costa et al.[28]	Modified Vaquette model, larger pores, CaP coating	Improved bone formation, fiber orientation, and vascularization.
Wang et al.[29]	Biphasic scaffold (collagen + Sr-doped Ca-silicate, extrusion)	Rabbit calvarial defects; enhanced osteogenesis.
Lee et al.[30]	Triphasic scaffold (cementum, PDL, bone), 3D-printed with PGA microspheres (amelogenin, CTGF, BMP-2)	Notable osteogenesis &fiber alignment, but discontinuous cementogenesis.
Rasperini et al.[1]	CT-based PCL + HA scaffold (SLS)	Large periodontal defects; exposure after 12 months reduced effectiveness.

XII. CUSTOM-DESIGNED 3D SCAFFOLDS FOR PERSONALIZED PERIODONTAL REGENERATION

A personalized medicine approach to periodontal regeneration emphasizes tailoring treatment to individual patient needs, accounting for specific pathological variations. This approach ensures optimal spatial guidance for progenitor cells, supports vascularization, and prevents unwanted epithelial downgrowth. To address these needs, 3D-printed scaffolds have emerged as a promising solution, offering the precision required for effective periodontal tissue engineering.

1) Design and Fabrication Using Medical Imaging: 3D printing technology allows for the creation of custom scaffolds based on detailed **medical imaging systems** like high-resolution cone beam CT scans. These scans provide the data necessary to design and fabricate scaffolds that precisely match the patient's unique anatomical features, improving the efficacy of regeneration.

2) Microchannel Architecture for Enhanced Regeneration: The incorporation of **microchannel architectures** within the scaffolds plays a crucial role in guiding **periodontal ligament fibers**, ensuring correct alignment and promoting better tissue integration. For scaffold fabrication, **polycaprolactone (PCL)** was cast using a wax mold, sterilized, and then seeded with **periodontal ligament cells (PDLCs)** before transplantation. This design helped to enhance the regeneration process by maintaining proper tissue orientation and providing structural stability.

3) Healing and Regenerative Outcomes:After **four** weeks of healing, custom-designed scaffolds showed significant improvements, including increased bone mass and mineral density, as well as better alignment of the regenerated periodontal ligament compared to random-pore amorphous scaffolds. Additionally, periostin expression at the treated site indicated enhanced tissue regeneration. During the periodontal surgery, the scaffold was pre-soaked in recombinant human platelet-derived growth factor BB to further promote healing.

While the scaffolds showed promise, challenges remain. After 12 months, clinical attachment gain and bone regeneration were observed in most cases. However, infection in one case led to complete scaffold removal after 13 months. Histological analysis and gel permeation chromatography revealed that 76% of the PCL molecular weight remained intact, which impeded bone formation and underscored the need for improvements in material degradation and biological integration.

To further enhance scaffold performance, research is focused on optimizing internal microstructures, selecting better polymer materials, and incorporating functionalization techniques.[31] In addition, bioprinting technology is being explored as a way to integrate living cells into hierarchical biofunctional structures. This technology mimics in vivo cell interactions, significantly improving the regenerative potential of scaffolds.

The ongoing development of photo-cross-linkable hydrogels such as gelatin-methacryloyl and poly (ethylene glycol) dimethacrylate as bioinks for 3D printing aims to enhance the printability, mechanical stability, and cytocompatibility of scaffolds. Although still in its early stages, bioprinting holds great potential for hierarchical regeneration, suggesting it will play an increasingly important role in periodontal tissue engineering in the future.[32]

XIII. CONCLUSION

3D printing and tissue scaffolds hold significant promise for advancing periodontal regeneration, offering the potential for precise, patient-specific therapies. However, complete tissue restoration remains a challenge. The selection of suitable biomaterials and the incorporation of bioactive components are crucial for optimizing scaffold functionality and improving tissue regeneration outcomes. Future studies should focus on refining these technologies to enhance their clinical relevance and therapeutic effectiveness. With the ability to fabricate scaffolds tailored to individual patient needs, 3D printing presents a promising approach to periodontal therapy. Despite current limitations, ongoing advancements in biomaterial development, scaffold engineering, and bioprinting are expected to pave the way for the successful translation of these innovations into clinical practice.

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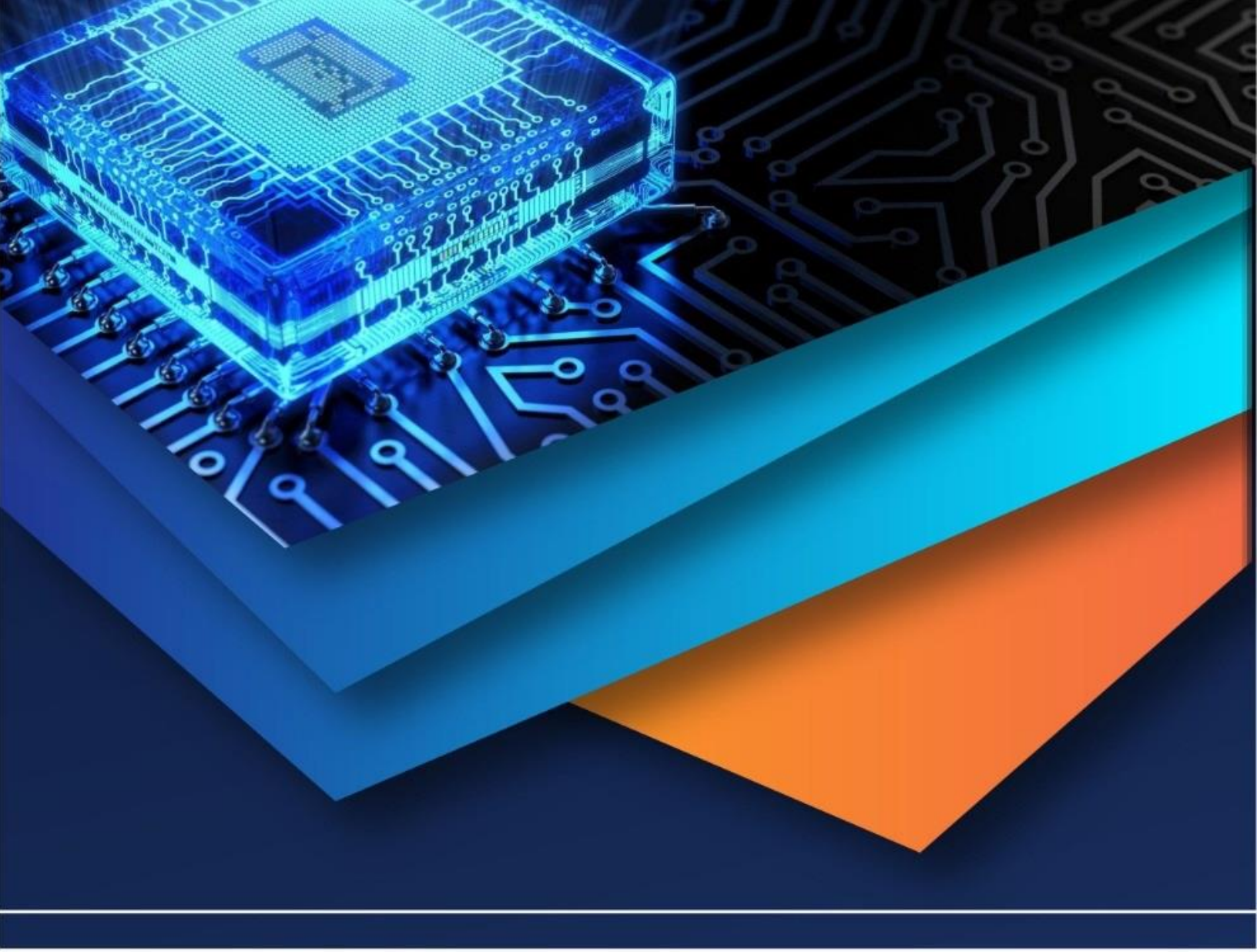

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