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Biomimicry revolutionizing dentistry: A review

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Abstract
"Biomimetics" is the field of science that uses the natural system of synthesizing materials through biomimicry. This method can be widely used in dentistry for regeneration of dental structures and replacement of lost dental tissues. Advancements in adhesive materials and understanding of biomaterial-tissue interactions at the nano and micro levels have led to the development of restorative materials that better mimic the color, morphology, and strength of natural teeth. Additionally, tissue engineering holds promise for regenerating lost or damaged dental tissues, replicating their natural counterparts. This review discusses various biomimetic approaches used in restorative dentistry, including biomaterials and tissue engineering techniques. We delve into the structure of teeth and the biomimetic properties of these materials. Biomimetic dentistry offers a transformative approach to dental care, with the potential to regenerate tooth structures and replace lost teeth entirely.

Keywords: Biomimetic materials, enamel regeneration, resin dentin bond

Introduction
Nature has always been a source of inspiration for human innovation. Biomimicry, which literally means "life imitating" in Greek, takes this concept a step further. It involves studying nature's successful designs and mimicking them to create new materials and technologies. Traditional biomaterials often lack the ability to seamlessly integrate with the body, potentially leading to implant failure. Biomimicry offers a solution by focusing on developing materials that mimic the functions and properties of natural tooth structures like dentin, enamel, and cementum. The ideal biomaterial in dentistry would possess similar mechanical, physical, and optical properties as natural teeth, while also replicating their physiological functioning. By harnessing the power of biomimicry, dental professionals can develop therapeutic approaches that are closer to natural biological structures and their functions. This review explores the exciting possibilities of biomimetic dentistry and its potential to revolutionize dental care.

The degree of biomimetic emulation possible can vary: [6]
Intact Periodontium: When the supporting bone structure (periodontium) is healthy and the teeth are vital and well-positioned, nature's morphology can be faithfully replicated. In these ideal cases, biomimetic principles can be fully applied.

Compromised Periodontium: In situations with a history of gum disease, narrow roots, or gaps between teeth, the periodontium may have lost its original form. Here, replicating nature exactly becomes less feasible. Irreversible losses may necessitate additional techniques within the restorations, such as optical illusions or morphological alterations (e.g., the miniwing concept for closing triangles). These techniques may not strictly adhere to biomimetic principles but are necessary to achieve optimal aesthetics and function in compromised cases.

Biomimetic Dentistry: Optimizing Restorations for Strength and Longevity
Biomimetic dentistry rests on four key principles: [1, 2]
1) Maximizing Bond Strength
2) Long-Term Seal

3) Preserving Pulp Vitality
4) Minimizing Residual Stress

Achieving Biomimetic Restorations: [1, 2]
Biomimetic dentistry utilizes specific protocols categorized as stress-reducing and bond-maximizing:

Stress-Reducing Protocols
Indirect/Semi-direct Restorations: These minimize residual stress and the amount of tooth structure removed.

Decoupling with Time: Minimizes stress on the developing bond by using thin initial layers of composite. This protocol states that polymerization shrinkage stress to the developing dentin bond of the hybrid layer should be minimized for a certain period of time (ie 5 to 30 minutes) by keeping initial increments to a minimum thickness (ie less than 2mm). Which prevents the connection, or "coupling," of deep dentin to enamel or superficial dentin before the hybrid layer is matured and close to full strength.

Thin Dentin Layers: Reduces stress by placing composite in small increments.

Reinforcing Fibers: Fibers within the restoration distribute stress and minimize its impact on the bond.
Slow-Start Polymerization: Reduces stress by slowing down the curing process of the composite material.

Low-Shrinkage Composites: Materials with minimal shrinkage minimize stress on the bond.

Dual-Cure Composites (Non-Vital Teeth): Chemical cure provides time for the bond to strengthen before full polymerization.
Dentin Crack Removal: Removes weak areas around the restoration to prevent future crack propagation.

Onlay Design: Thinner onlay cusps minimize tensile stress on the bond.

Verticalized Occlusal Forces: Redirects forces for better stress distribution.

Bond-Maximizing Protocols
Caries-Free Zone: Ensures a strong bond by creating a healthy dentin area around the restoration.
Repairing Existing Composite Restorations: Surface modification techniques enhance bonding to existing composite material.

Enamel Beveling: Increases the surface area for bonding.
Matrix Metalloproteinase Deactivation: Preserves bond strength by preventing its degradation.
Gold-Standard Dentin Bonding Systems: Utilizes high-performance bonding agents.

Immediate Dentin Sealing: Bonds the dentin at the preparation stage for a stronger connection.
Resin Coating: Protects the dentin bond and creates a secure foundation for the restoration.

Supragingival Margins: Elevates margins above the gum line for optimal bonding.
By implementing these protocols, biomimetic dentistry aims to achieve predictable, long-lasting restorations that preserve natural tooth structure and function.

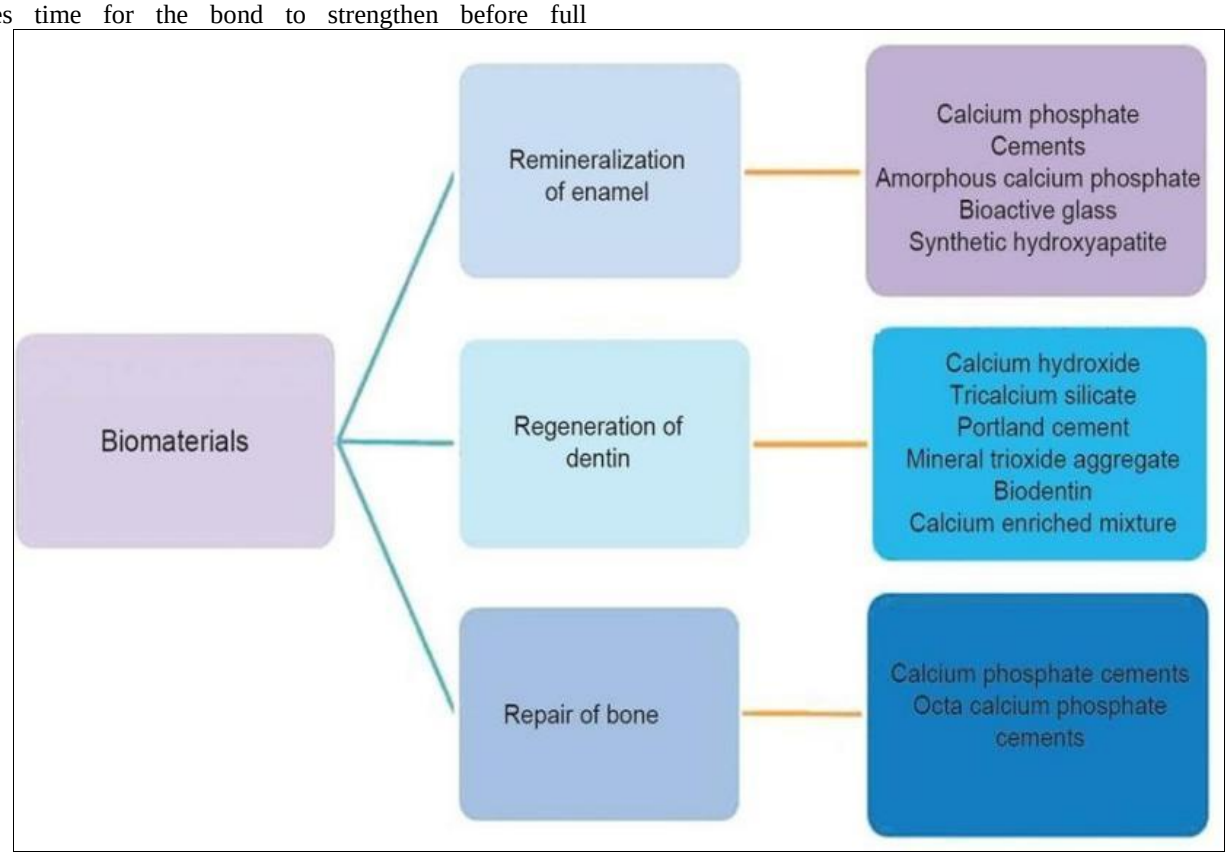

Fig 1: Based on Biomineralization: [7]

Biomimetic Materials: A New Frontier in Restorative Dentistry; Biomimetic materials are designed to align with several key properties of the tooth structure they are replacing:

Glass Ionomer Cements (GICs): [8] These chemically bond to tooth structure, release fluoride to prevent decay, and boast a thermal expansion coefficient similar to natural teeth.

Self-healing Composites: [9] These innovative composites contain microcapsules filled with resin. Upon cracking, the capsules release resin, filling the crack and initiating self-repair.

Calcium Hydroxide ($Ca(OH)_2$): [8] This antibacterial material promotes the formation of tertiary dentin, a protective layer beneath damaged areas.

Mineral Trioxide Aggregate (MTA): [8, 10] This biocompatible material exhibits excellent adhesion to dentin, stimulates dentin bridge formation, and has superior sealing properties compared to $Ca(OH)_2$.

TheraCal: [8, 10] Light-cured resin with calcium silicate fillers for high calcium release.

Generex A & B: [11] Calcium silicate-based materials for root-end fillings with good handling properties and washout resistance.

Doxadent: [8, 10] Calcium aluminate-based cement with good biocompatibility but lower wear resistance compared to composites.

Ceramir: [12] Another calcium aluminate material used for permanent cementation of dental restorations.

Hydroxyapatite (HA): [10] This biocompatible material resembles bone composition and promotes bone bonding. However, its low mechanical strength limits its use in load-bearing areas.

Calcium Phosphate Cement (CPC): [8, 10] This moldable material forms hydroxyapatite upon setting and offers good handling properties.

ACP Technology: [10] This delivery system containing calcium and phosphate aids in tooth remineralization.

Tricalcium Phosphate (TCP): [10] This osteoconductive material promotes bone growth and has applications in tooth remineralization.

Bioactive Glass: [13] is a special material used in dentistry to mimic natural teeth. It can release fluoride to strengthen tooth enamel and fight cavities, especially in the early stages. This glass also helps make teeth stronger and fills in tiny holes where minerals have been lost. On top of that, it creates a smoother surface on the tooth, making it harder for bacteria penetration. These glasses bond with bone and stimulate bone formation, making them useful for bone grafts and managing dentin hypersensitivity.

Emdogain: [10, 13] An enamel matrix derivative product that mimics natural tooth development processes and promotes periodontal tissue formation.

Platelet-Rich Fibrin (PRF) Membrane: [10,14] This biocompatible membrane containing platelets, growth factors, and fibrin enhances wound healing.

Optimizing Restorations with Biomimetic Materials: Balancing Mechanics and Biology

A crucial aspect of biomimetic restorations lies in mimicking the complex interplay between enamel and dentin. Enamel, the hard, brittle outer layer, protects the tooth from wear and tear. Dentin, the softer, resilient inner layer, provides cushioning and shock absorption.[15] Biomimetic materials should strive to replicate these properties:[16]

Enamel Replacement: Ideally, the restorative material replacing enamel should be:

Brittle and hard

Glass-like and translucent

Possess an elastic modulus (EM) comparable to natural enamel (72-125 GPa)

Dentin Replacement: The material chosen to replace dentin should exhibit:

Resilient properties

An EM closer to natural dentin (14-38 GPa)

Matching the material's stiffness to that of the specific tooth region (enamel, dentin, etc.) is crucial for optimal function and stress distribution

Bioactivity: A Hallmark Feature

A crucial property of biomimetic materials is their bioactivity. Hench classified bioactive materials into two categories:[17]

Rapid Surface Reaction: These materials undergo a rapid surface reaction, triggering an intracellular and extracellular response. This reaction facilitates bonding between the material and both hard and soft oral tissues.

Slower Surface Reaction: Materials in this category exhibit a slower surface reaction, primarily inducing an extracellular response.

Remineralization and Dentin Protection: [18]

Bioactive materials play a significant role in remineralization, the process of restoring lost mineral content in the tooth structure. They achieve this through several mechanisms: Bioactive materials can participate in the ionic exchange, leading to the supersaturation of surrounding fluids. This supersaturation promotes the precipitation of ions within demineralized tissues, facilitating the formation of hydroxyapatite crystals. Bioactive materials can strengthen the collagen mesh within the tooth structure. This not only improves the remineralization process but also enhances the mechanical properties of the tooth.

Antibacterial Effects: [19, 20]

Certain materials can elevate the local pH to a range between 8 and 9. This alkaline environment inhibits bacterial growth.

Adhesion – The Cornerstone of Biomimetic Restorations:

Effective bonding creates a strong connection between the restorative material and the tooth, mimicking the natural structure and functionality.

Challenges to Bond Durability: [21]

Water absorption weakens the adhesive interface over time through hydrolysis. Enzymes, particularly matrix metalloproteinases (MMPs), can break down collagen within the adhesive layer.

Strategies to enhance resin dentin bond

Improving E&R and SE bonding by non-thermal atmospheric plasma treatment (for both E&R and SE): [22]

The exploration of non-thermal atmospheric plasma (NTAP) as a method to improve bonding to dentin presents an intriguing possibility. NTAP, a partially ionized gas containing excited atoms and molecules, offers theoretical advantages for dental adhesion. These highly reactive particles could promote cross-linking and generate functional groups on the dentin surface, potentially enhancing wettability, resin polymerization, and penetration. Additionally, free radicals or peroxides deposited by NTAP may activate the dentin surface, fostering a stronger interaction between adhesive monomers and collagen.

Biomimetic Repair of E&R Hybrid Layers: The concept of biomimetic repair of etch-and-rinse (E&R) hybrid layers, introduced by Tay and Pashley in 2008. This technique employs a guided tissue-remineralization process to address the degradation of exposed collagen within incompletely resin-infiltrated E&R interfaces.

While the research successfully demonstrated intra- and interfibrillar remineralization after several months, the direct clinical application of this biomimetic strategy remains questionable. The logic behind aggressively demineralizing dentin with phosphoric acid (a core step in E&R bonding) only to subsequently embark on a complex and time-consuming remineralization protocol seems counterintuitive.

Moreover, the well-established effectiveness of self-etch (SE) adhesives presents a simpler alternative. SE adhesives partially demineralize dentin, preserving a significant portion of the surrounding collagen matrix. This inherent protection offered by SE bonding eliminates the need for a subsequent remineralization step.

However, the success of remineralizing E&R hybrid layers underscores the inherent vulnerability of these interfaces to degradation. Ideally, fully resin-saturated E&R hybrid layers should resist remineralization attempts. This highlights the potential for this technology to inform the development of minimally invasive restorative materials with built-in remineralization capabilities. Such materials could potentially reduce the need for complete caries removal, particularly in deep lesions with a high risk of pulp exposure [21].

Ethanol Wet-Bonding: The Gold Standard: Ethanol wet-bonding stands out as a potentially superior approach to improve resin infiltration and interdiffusion within the E&R bonding process. This strategy hinges on meticulously replacing water within the exposed collagen network with ethanol. Ethanol, compared to water, acts as a superior solvent, facilitating deeper diffusion of resin monomers, particularly those with hydrophobic properties, into the demineralized dentin created by phosphoric acid. The process necessitates multiple ethanol applications over several minutes, posing a challenge for practical implementation in a clinical setting [23].

Inhibition of enzymatic biodegradation: Matrix metalloproteinases (MMPs) are enzymes known to degrade extracellular matrix proteins. While their activity in adult dentin is generally low, they have been implicated, along with cysteine cathepsins, in the biodegradation of adhesive-dentin interfaces. However, the precise contribution of MMPs to bond degradation remains unclear. Water sorption and its consequent hydrolytic effects seem to be the primary culprits behind bond deterioration. Furthermore, data on MMP activation by different adhesives and the effectiveness of MMP inhibitors are inconsistent [24].

Studies suggest that phosphoric acid etching, a core step in E&R bonding, readily exposes and activates MMPs, while this effect is less pronounced with SE adhesives. Chlorhexidine digluconate (CHX), a common MMP inhibitor, has been incorporated into etching agents, adhesives, and used as a standalone solution following etching. While CHX shows promise in maintaining bond stability for short periods (up to 6 months), its effectiveness diminishes over longer durations (1 year and beyond). This suggests that MMP inhibition may slow bond degradation but doesn't prevent it entirely, as hydrolysis continues to play a role. This technique allows for precise localization of proteolytic activity at the adhesive interface. Studies employing in-situ zymography have shown a reduction in collagenolytic activity at the interface when MMP inhibitors are used [25,26].

Dentin biomodification by collagen cross-linking: Dentin biomodification using collagen cross-linkers presents a promising strategy to improve the durability of E&R bonds. This approach goes beyond simply inhibiting matrix-bound enzymes (MMPs). It aims to strengthen the very foundation of the bond by enhancing both intra- and intermolecular cross-links within the collagen network. Essentially, this renders the collagen more resistant to biodegradation, leading to a more stable interface.

Researchers have explored both synthetic and naturally derived collagen cross-linkers. Their primary target is the demineralized, collagen-rich layer created by E&R adhesives. By fortifying these E&R hybrid layers, the treatment aims to improve their biochemical and biomechanical properties. This translates to enhanced resistance against enzymatic degradation and improved overall bond strength.

The concept behind collagen cross-linking revolves around creating additional inter- and intramolecular cross-links within the dentin matrix. This reinforcement is achieved by applying extrinsic cross-linking agents, leading to increased resistance to enzymatic breakdown and improved tensile strength. Studies have shown that various cross-linkers, such as proanthocyanidin and particularly glutaraldehyde, can indeed promote bond strength when applied for varying durations (10 minutes to 40 hours) [27].

Table 1: Cardol and Cardanol

Types of biomodification	Bio-modifiers
Physical Methods	Riboflavin with ultraviolet radiation
Chemical agents	Glutaraldehyde
	Carbodiimide
Synthetics	Chitosan
	Curcumin
	Proanthocyanidin
Naturals	Cardol and Cardanol
	Epigallocatechin 3-gallate
	Extract of the aroeira

Optimizing Adhesive Polymerization for Durable Bonds: Achieving optimal polymerization of dental adhesives is paramount for creating long-lasting, stable interfaces. A well-polymerized adhesive layer forms the foundation for a successful restoration.

Considerations for maximizing adhesive conversion: Always light-cure the adhesive layer independently and immediately after application to dentin (and enamel). This minimizes water

uptake from underlying dentin through osmosis, a process that can compromise bond strength. For direct restorations, apply the adhesive in a visibly thick layer. This creates a stress-absorbing layer, enhancing bond durability. For indirect restorations using E&R/SE-assisted composite cements, thoroughly air-thin the adhesive until it no longer flows or pools before light curing. This ensures proper seating of the restoration without compromising the adhesive layer. Light curing the adhesive independently prior to luting the restoration further improves bond strength. Modern universal adhesives (UAs) typically form thin films (around 10 microns), minimizing the space occupied by the adhesive layer and allowing for good seating of well-fitting restorations. When employing an IDS approach before luting, avoid air-thinning the adhesive. Apply it in a thick layer similar to direct restorations. This layer can be further stabilized with a flowable composite. Since the conventional or digital impression is taken after the IDS procedure, there's no risk of compromising restoration fit.

The final adhesive interface should be as hydrophobic as possible to minimize water sorption, a key factor in bond degradation. Adhesives should be formulated with effective photo-initiator systems and a well-balanced monomer composition. This includes optimizing the ratio of mono/bi-functional monomers to cross-linking monomers for optimal polymerization. Evaluate adhesives for water solubility and water sorption over time. Additionally, assess their intrinsic mechanical properties, such as ultimate tensile strength and fracture toughness, considering the plasticizing effects of water uptake [21, 28].

Enhancing Bond Durability with Extra Hydrophobic Resin Sealing: Extra hydrophobic resin sealing offers a practical approach to improve the performance of dental adhesives, particularly simplified single-solution adhesives and universal adhesives (UAs). This technique involves applying an additional layer of highly hydrophobic resin over the primary adhesive layer. The benefits are three-fold: Increased Hydrophobicity, Improved Polymerization Efficiency, Enhanced Interface Stability.

Extensive research supports the bond-promoting effect of this technique for both E&R and SE bonding modes. Essentially, it mimics the effect of adding an additional bonding layer, transforming a 2-step E&R into a 3-step E&R, a 1-step SE into a 2-step SE, and a single-step/two-step E&R/SE UA into a two-step/three-step E&R/SE UA. This translates to improved durability by retarding bond degradation [21].

Primary ionic bonding: Self-etch adhesives (SEAs) and many modern universal adhesives (UAs) rely on functional monomers to achieve micromechanical adhesion to tooth structure. These (bi-)functional monomers possess a unique three-part structure: Acidic Functional Group, Spacer Group & (Meth)acrylate Group [29].

The acidic group forms a weak electrostatic interaction with Hap (Hydroxyapatite), followed by potential stable chemical bonding through the formation of monomer-calcium salts. This results in a submicron HAp-rich hybrid layer with minimal collagen exposure, promoting a more durable interface. Stronger SE adhesives (and E&R adhesives) follow this route, leading to a deeper demineralized zone with exposed collagen fibrils. However, this approach can destabilize the interface due to a lack of strong chemical bonding and increased susceptibility to hydrolytic degradation [30].

10-MDP is a highly effective functional monomer known for its strong ionic bonding with HAp, forming stable 10-MDP-Ca salts. Additionally, research suggests that 10-MDP self-assembles into nanolayers, further contributing to bond strength and durability. This is supported by both laboratory and clinical data, particularly the positive long-term performance of 10-MDP-based adhesives like Clearfil SE Bond [31].

Enamel Regeneration: Challenges and Hope

Unlike most tissues, tooth enamel cannot regrow after eruption. This presents a significant challenge for dentistry. Regenerating enamel would require overcoming several hurdles:

Enamel development involves extreme mineral concentrations and pH shifts, difficult to replicate in-vitro. Ameloblasts, the key cells for enamel formation, are challenging to culture and maintain functionally outside their natural environment. Recreating the intricate structure of natural enamel, with its precisely aligned crystals and interwoven bundles, remains a significant hurdle.

Despite these difficulties, researchers are exploring promising avenues Developing synthetic enamel-like materials that mimic the structure and properties of natural enamel.

Refining techniques to culture and maintain functional ameloblasts or their precursors for enamel matrix production.

Exploring entirely new approaches to overcome current limitations [32].

Organic matrices mediated mineralization

Many biological materials, like tooth enamel, form through a process called organic matrix-mediated mineralization. This approach differs from simple crystal growth in solution. Here, organic molecules act as templates, guiding the assembly of mineral nanoparticles into highly organized structures. This "oriented attachment" allows for precise control over crystal size, shape, and orientation [33].

Recombinant Amelogenin: This main protein in the enamel matrix controls crystal growth and orientation. Studies show it binds preferentially to specific crystal faces, leading to elongated, ribbon-like crystals. Combining amelogenin with mineralization inhibitors further refines crystal size and shape [34].

Leucine-Rich Amelogenin Peptide (LRAP): This smaller version of amelogenin mimics its properties. LRAP stabilizes amorphous calcium phosphate and induces the formation of needle-like crystals with a parallel orientation [35].

Human Dentine Phosphoprotein (DPP): Found in dentine, DPP captures calcium and phosphate ions, influencing crystal growth and orientation. Researchers are exploring peptides containing DPP's key sequences to regulate enamel regeneration [36, 37].

Dendrimers: versatile artificial polymers, are being explored for enamel regeneration. These molecules resemble natural proteins and can be modified with various functional groups. Studies show promise with PAMAM dendrimers. Their charged groups interact with growing enamel crystals, influencing their orientation. Further modifications, like attaching alendronate (ALN), can strengthen this interaction and promote the formation of elongated crystals, similar to natural enamel. Another approach uses dendrimers modified

with L-aspartic acid. These self-assemble into structures mimicking amelogenin, a key protein in enamel formation. These assemblies influence crystal growth, leading to oriented crystal filaments [38].

Surfactants: molecules with both water-loving and oil-loving ends, can influence how minerals form. They self-assemble into tiny structures called micelles, which act as templates for growing crystals [39].
There are two main types of surfactants: ionic and non-ionic.

Nonionic Surfactants: These weakly interact with calcium ions, offering limited control over crystal growth.

Ionic Surfactants: These strongly bind calcium ions, influencing crystal shape and orientation. A common example is Bis (2-ethylhexyl) sulfosuccinate sodium salt (AOT), which forms plate-like structures that guide crystal growth along a specific axis.
By adjusting the ratio of water to surfactant and adding other molecules, scientists can fine-tune the micelles structure and control crystal formation. This approach allows for the creation of elongated crystals similar to those found in natural enamel. Ionic surfactants, like disodium oleoamido PEG-2 sulfosuccinate (SPEG), also show promise in mimicking the enamel formation process [40, 41].

Template of the cation membrane system: Cation-selective membranes can mimic calcium ions (Ca^{2+}), which promotes the lengthwise growth of enamel crystals. These membranes are made of a material that controls the direction of Ca^{2+} transport. Crystals grown on this membrane are longer and more organized than crystals formed in solution.
Another factor influencing crystal growth is the hydrogel matrix. This gel mimics the enamel matrix, which is composed of enamel proteins. When a gel is used on one side of the membrane, it promotes the formation of elongated crystals compared to crystals grown without a gel. This is because the gel creates a steady flow of ions that encourages crystal orientation and lengthwise growth.
Finally, the flow of ions and the pH value also affect the shape of the crystals. Higher concentrations of Ca^{2+} and phosphate ions (PO_4^{3-}) lead to larger crystals. Lower pH values and PO_4^{3-} concentrations promote growth in a specific direction. Cation-selective membranes provide a promising approach for mimicking the natural process of enamel formation [42,43].

Electrolytic deposition (ELD): Enamel forms under a tightly controlled pH environment. During the initial stages, acid byproducts from crystal formation lower the pH. Ameloblasts, special cells, counteract this with an acid-base transport system, maintaining a neutral pH for optimal crystal growth.
Electrolytic deposition (ELD) mimics this process using an electrical current. At the cathode (negatively charged electrode), water is converted to hydroxyl ions (OH^-), which neutralize excess acid and raise the local pH. This promotes hydroxyapatite crystal growth and regulates amelogenin assembly, a key protein in enamel formation.
Studies have shown success in creating enamel-like structures using ELD. As the pH rises at the cathode, amelogenin self-assembles into structures that guide the formation of calcium phosphate crystals on the electrode surface.
While safe and capable of accelerating mineral deposition, ELD has limitations. The process is slow, producing thin layers of minerals over several hours. Additionally, its effectiveness in a clinical setting remains unclear [44].

Conclusion
The future of dentistry seeks to regenerate teeth or create self-healing materials. Promising biomimetic approaches for enamel and dentin repair are in early stages, but their clinical use would revolutionize the field. Biomimetic technologies offer possibilities for better adhesion, dentin integration, and sealing. Research on innovative biomaterials and biomolecules for tooth regeneration is ongoing, with the ultimate goal of completely mimicking natural teeth.

Conflict of Interest
Not available

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Not available

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