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From biomimetics to smart materials and 3D technology: Applications in orthodontic bonding, debonding, and appliance design or fabrication

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ABSTRACT

This review covers aspects of orthodontic materials, appliance fabrication and bonding, crossing scientific fields and presenting recent advances in science and technology. Its purpose is to familiarize the reader with developments on these issues, indicate possible future applications of such pioneering approaches, and report the current status in orthodontics. The first section of this review covers shape-memory polymer wires, several misconceptions arising from the recent introduction of novel three-dimensional (3D)-printed aligners (mistakenly termed shape-memory polymers only because they present a certain degree of rebound capacity, as most non-stiff alloys or polymers do), frictionless surfaces enabling resistance-less sliding, self-healing materials for effective handling of fractured plastic/ceramic brackets, self-cleaning materials to minimize microbial attachment or plaque build-up on orthodontic appliances, elastomers with reduced force relaxation and extended stretching capacity to address the problem of inadequate force application during wire-engagement in the bracket slot, biomimetic (non-etching mediated) adhesive attachment to surfaces based on the model of the gecko and the mussel, and command-debond adhesives as options for an atraumatic debonding. This review's second section deals with the recent and largely unsubstantiated application of 3D-printed alloys and polymers in orthodontics and aspects of planning, material fabrication, and appliance design.

1. Introduction

Advances in the field of biomimetics, termed from the greek $\beta\iota o$ -bio meaning living and $\mu i \mu \eta \sigma \iota \varsigma$ -mimetic (adjective, meaning imitating/copying), have brought a significant growth in material development and applications. Despite numerous patents and substantial breakthroughs in biomedical or engineering materials, the orthodontic profession has yet to explore the feasibility of introducing such biomimetic materials in clinical practice.

The purpose of this comprehensive review is to familiarize the reader with these developments, indicate possible applications of such pioneering approaches in the introduction of materials/processes in the broader field of biomedical or engineering/industrial materials, and report the status of applications in orthodontics.

The first section of this review covers:

a.shape-memory polymer wires, aiming to clarifying several misconceptions arising from the recent introduction of three-dimensional (3D)-printed aligners, mistakenly termed shape-memory polymers only because they present a certain degree of rebound capacity, as most non-stiff alloys (multistrand wires) or polymers do.

b.frictionless surfaces enabling resistance-less sliding.

c.self-healing materials for effective handling of fractured plastic/ceramic brackets.

d.self-cleaning materials to minimize microbial attachment and plaque build-up on bracket, aligner, wire, and elastomers.

e.elastomers with reduced force relaxation and extended stretching capacity to address the problem of inadequate force application during wire-engagement in the bracket slot.

f.biomimetic, non-etching mediated, adhesion based on the gecko or mussel model.

g.command-debond adhesives as options for an atraumatic debonding.

The clinical challenges for each issue will be discussed followed by corresponding advances in material manufacturing and the introduction of a relevant application in technology and industry.

The second section of this review deals with the recent and largely unsubstantiated application of 3D-printed alloys and polymers in orthodontics and aspects of planning, material fabrication, appliance

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design.

2. Biomimetics and smart materials

2.1. Shape-memory polymers

2.1.1. Clinical challenge

The clinical problem that led to the development of polymeric or surface-altered wires is the aesthetic problems from the use of metallic wires.

Earlier attempts to introduce solid plastic polymeric wires such as Optiflex (Ormco Co., Glendora, CA) for the initial treatment stages resulted in the application of polymers with reduced modulus of elasticity, stiffness, but also low resilience and thus low elastic energy stored in the wire (which in the stress-strain curve is provided by the area under the curve until the yield point, or the so called 'range')—precluding their use in most cases with average crowding. Moreover, their low bending stiffness adversely affected their levelling capacity [1]. This is different from the aligning properties of the wire as the bent wire in the buccal segment of deep curve of Spee cases needs have high bending stiffness and cross sections filling the edgewise size of the bracket, i.e., 0.018- or 0.022-inch. This contradicts the false notion that Nickel-Titanium (NiTi) wires were introduced exactly because with their low modulus can effectively level the curve of Spee. A round 0.016-inch stainless steel much higher stiffness than Titanium-Molybdenum-Alloy (TMA) wires of any cross-section or shape. Similarly, rectangular 0.016×0.022 -inch NiTi and TMA wires to level the occlusion in the straightwire technique also face the problem of reduced bending stiffness owing to the reduced contribution to this effect of the flatwise dimension of the wire, in addition to the fact that they show play in the edgewise dimension (in the 0.018-inch system).

Other plastic wires were developed in the late 1990's-early 2000's by BioMers Products, LLC (Jacksonville, Fla) to address these concerns and efficiently align / derotate teeth, but their hydrolytic degradation after extended periods of time precluded their widespread use.

2.1.2. Available materials

Developed in the mid 2000's, shape-memory polymers—which have nothing to do with the claimed memory properties of recently introduced 3D-printed aligners—were introduced initially for biomedical applications. Exposure of initially developed polymer threads to heat or to a specific wavelength of light [2,3] resulted in modification of their shape to their pre-engineered shape. Therefore, thrombectomies and removals of vessel clots were facilitated through the catheterization of the vessel with a shape-memory thread, which after being navigated through the thrombus, had its external to the patient's body part exposed to a specific stimulus that reverted the thread to its initial shape (in that case of a cork), thereby facilitating clot removal.

However, this application has since 2005 not yet received any consideration for use in orthodontic wires or orthodontic aligner applications.

2.2. Frictionless movement

2.2.1. Clinical challenge

Friction, although often overemphasized, plays a significant role in determining the magnitude of force applied to the tooth crown through an activated wire or a prescription bracket. It has also been shown to be an impeding factor against effective tooth movement and efforts to overcome this included the use of wires with smoother surfaces or alternative ligation modes such as self-ligation, which however have never associated with improved tooth movement rates in vivo. The problem lies with factors traditionally ignored in oversimplified in vitro studies, such as the specific tooth movement pattern (which deviates from the straight line path and includes several tilting spatial alterations) and the in vivo ageing of the involved materials (bracket, wire,

ligature) that greatly affect exerted forces.

2.2.2. Available materials

A possible solution to the abovementioned problems might come from broader industrial metallurgical applications mimicking the flaked surface texture of snakes. These reptiles show remarkably smooth movement across various terrains, owing not to the smooth surface of their skin, but to the textured pattern and the specific arrangement of their external flake layers [4].

Relevant research has demonstrated that the friction coefficient of textured surfaces of snakes with a characteristic orientation of the superimposed skin flakes was almost 50% reduced compared to the modeled untextured one.

Steel surfaces used in industry or manufacturing made to resemble the snakes' external flake layer were built at the end of the first decade of 2000 and were met with success but have yet to be introduced in orthodontics.

2.3. Self-healing materials

2.3.1. Clinical challenge

Ceramic, and to less extent plastic, brackets were introduced as an appliance with superior aesthetics, but several issues arose from their large-scale clinical use. Most research on this topic is focused on their fracture strength and debonding characteristics, due to their unfavorable debonding pattern that was reported in the early 1990 s [5]. The observation that ceramic brackets fracture frequently, usually at the wings and most often during debonding, is universal knowledge for most readers. These materials are composed of atoms bound together with such strong forces that their flexibility is notably impaired. As a result, force application on them leads to a minimum elastic deformation and no permanent deformation. It follows that these materials maintain their dimensions / shape after fracture, as no deformation has set in, due to their bonding energy and strong directional characteristics. Also, the atomic packing factor of such materials is high, implying that their dense atomic distribution in 3D arrays results in high crystal density. Therefore, no plastic deformation of the wings is possible and, when the force exceeds a certain value, the wing fractures.

2.3.2. Available materials

These issues led to interest being attracted to the production of self-healing polymeric materials, owing to the potential flexibility in synthesizing polymers with desirable properties. One of the first such attempts involved including monomer-filled spheres, which upon crack propagation would empty their content to the fracture vicinity to facilitate filling of the fracture path with an auto-polymerized material. Later applications, which have already been adopted by the industry, include the development of self-healing of oxetane-chitosan compounds in the form of coatings that, upon exposure to ultraviolet sunlight, initiate a cascade of events bringing these two molecules together to form a coating that closes potential damage of the initially formed coating. This found applications in the automobile industry, with protective car coatings already being marketed.

In the area of ceramics, development of such materials is more challenging as the necessity of altering ceramic structural defects usually requires high temperatures, which exceed the intraoral spectrum. In as much, additional processes such as application of combustion chambers [6] or electric field-induced colloidal aggregation [7] to fill cracks and inhibit propagation, thereby avoiding a catastrophic failure, have no feasible application mode in orthodontics. Therefore, despite the advances in that field, the potential application to orthodontic materials involves only polymeric products (brackets and aligners), which on the other hand, are ductile and present a much lower clinical failure incidence.

2.4. Self-cleaning materials

2.4.1. Clinical challenge

Plaque accumulation on a biomaterial exposed to a biological system is accompanied by the organization of a non-cellular biofilm by spontaneous adsorption of extracellular macromolecules, composed mostly of glycoproteins and proteoglycans. These films induce a conditioning effect that modifies the biomaterial's surface properties and alters both the response of the subsequently attached cells and the interactions occurring at the biomaterial-host interface. This conditioning effect is based on the differing capacities of artificial surfaces to fractionate proteins from biological fluids, such as saliva or blood, and the ability to induce conformation and orientation changes of adsorbed proteins.

The outcome of biofilm adsorption is dependent on the biological fluid flow rate at the site of contact, the type of interfacial interactions involved, and the attachment strength with the substrate. Under static conditions or low flow rates, the biomaterial surface chemistry is the fundamental factor affecting the composition and organization of acquired biofilms, whereas in environments with high flow rates, substrate surface molecular motion and roughness are also important factors. In addition, with long exposure periods, material properties such as porosity, sorption, corrosion, and biodegradation further modify biomaterial-host interactions. Finally, the material's wettability is modulated by its critical surface tension and plays a significant role in the development of adverse effects either on the tooth's enamel (in the form of white spot lesions) or periodontal inflammation.

2.4.2. Available materials

Most efforts in this field have concentrated around the alteration of the wetting characteristics of orthodontic materials such as brackets adhesives and elastomers. The problem with adhesives lies with the fact that a reduced wettability to disrupt the developed biofilm on the microbia-attracting adhesive margins, would also result in reduced wetting of the enamel etching-induced tags and projection of the resin in the enamel, thus adversely affecting the bond integrity of the bracket to enamel.

Potential solutions for brackets or elastomers could be their manufacturing with reduced wettability modelled by the lotus effect [8], which is based on the example of the synonymous plant that, through a dense network of hairs developed on its surface, allows the formation of a large contact angle, which is indicative of reduced wetting (Fig. 1).

The formation of superhydrophobic surfaces has been adopted in medicine [9], dentistry [10], and everyday applications ranging from utility material surfaces, dishes, handles, car surface coatings of cars to decrease dirt, and fabric repellant surfaces, among others.

In orthodontics, the fabrication of self-healing brackets [11] has



Fig. 1. A sign of reduced wettability. Note the high contact angle arising from the formation of a high meniscus of liquid on the substrate. This wetting reduces the formation of biofilm, which is the first step for the adherence of plaque and colonization of the surface by microbia. This model is pursued to be applied to brackets and elastomers to reduce plaque accumulation on appliances.

involved the development of Titanium photocatalysis [12], which involves the coating of the bracket with a layer of Ti oxide that upon sunlight exposure releases reactive oxygen species or hydroxyl radicals, which have antimicrobial, odor-removing effects. However, such applications have yet to be widely employed in orthodontics.

2.5. New elastomers

2.5.1. Clinical challenge

The use of polyurethane-based elastomeric ligatures and modules in engaging archwires and closing spaces in orthodontics is accompanied by a notable force relaxation that accounts for up to 40% of the initially applied load. This effect is accentuated by the laborious and multiperspective intraoral ageing pattern of these polymers that comprises of hydrolytic degradation, swelling, and softening, which further degrade the mechanical properties and decrease the exerted forces from the material. At the same time, they favor plaque build-up and contribute to the microbial colonization of the bracket-wire-elastomer complex. Elastomeric force relaxation derives from the material's macroscopic degradation in the form of tearing of the structural surface and bulk structure, presenting discontinuities because of sustained load. Microscopically, the extension of the molecular chains that, in some cases fracture, leads the load to be exerted by fewer number of bearing units, and as a result presenting higher deformation.

Efforts to address this problem in the broader biomedical literature have focused on increasing the crosslinking of chains or their length to provide more area for load-distribution and longer chains. The problems arising from these approaches have to do with the increased initial stiffness in the cases of fortifying the crosslinking (which would result in increased exerted forces) and the entanglement in the scenario of incorporating much longer chains which cause the noodle effect—i.e. the increase in stiffness due to the perplexed structure and the entanglement of chains.

Thus, ideally elastomers should maintain the applied load for at least 4–6 weeks, while they should be hydrophobic to reduce the attraction of species and be water tolerant.

2.5.2. Available materials

Elastomers used in industrial applications are structures with chains forming multi-dimensional networks [13,14]. As a result, these elastomers have much higher toughness and strength, producing extension ranges in the order of 50 times the original length (in general rubber elasticity refers to a property of a material to be capable of being extended 10 times its size).

An alternative approach could be engaging the wire tying a silk fiber around the bracket wings, as silk has remarkable properties [15] and has recently been produced synthetically [16], leading to a product stronger than Kevlar and more elastic than nylon.

2.6. Biomimetic adhesives

2.6.1. Clinical challenge

Etching-mediated orthodontic bonding and consequently debonding is basically an interventional procedure that irreversibly alters enamel structure, roughness, and composition by introducing resin tags into the enamel structure. These formations remain after debonding and constitute a substrate where a series of effects such as decalcification and color alteration take place. The latter might also be attributed to the polymerization shrinkage that leads to detachment of resin-tags from the enamel walls, thereby allowing the penetration of colorants from the oral environment or corrosion products of the welded mesh of the bracket base, leaving characteristic black spots on the adhesive.

Along with glass-ionomer bonding that is associated with reduced adhesive penetration depths, alternative methods have been developed in the biomedical literature for bonding of tissues and materials.

2.6.2. Available materials

In the mid-2000's, efforts to replicate the ability of some animals to sustain their bodies against gravity were developed, using the lizard gecko as a model (Fig. 2). Analysis of the gecko's feet identified a dense hair-network, which increased substantially the effective contact area of the foot to the underlying surface providing a mechanism such as Velcro materials [17]. These surfaces were used as a model to fabricate carbon nanotube networks embedded into a polymer surface [18]. In addition to this mechanism, and with the objective of facilitating bonding to wet surfaces, the mussel model was adopted [19], as the latter have the ability to bond chemically to a number of dissimilar surfaces ranging from rock to wood or metal. The resulting adhesive synthesized was patented as geckel [20], a biomedical product which can be applied as substitute of deep layer stitching instead of sutural materials.

These biomimetic adhesives could become a standard, introducing a bonding method without irreversible effects on enamel and, ideally, without the necessity of applying rotary instruments for the removal of adhesive remnant.

2.7. Command-debond adhesives

2.7.1. Clinical challenge

Debonding of orthodontic appliances and attachments involves several traumatic procedures, which include the use of rotary instruments to remove the polymerized adhesive that was transformed into a crystalline structure from its initially viscous pre-polymerized form. This exposes enamel to alteration risks in the form of groove formation from the rotating bur (Fig. 3), potentially affecting the enamel's color parameters and gloss. The aforementioned process induces irreversible damage to enamel regardless of the etching-mediated process, i.e., the presence or resin tags after debonding and resin removal. Therefore, introducing a method that enables atraumatic appliance removal constitutes an independent variable offering the possibility to minimize some of these enamel adverse effects.

2.7.2. Available materials

Polymeric adhesives have been experimentally synthesized for industrial applications by adding iron fillers. Orthodontic adhesives usually contain fillers in a ratio of 0.6–0.7 (% wt) in the form of silica particles or barium glasses, which possess a refractive index of 1.55 at the wavelength of the photoinitiator. Evidence available on the field of resin composites suggests that maximum light scattering occurs at particle sizes equivalent to the half of the wavelength of the polymerization photoinitiator, which for camphorquinone systems is 468 nm—hence a favorable filler size would be about 230 nm. However, the typical microscopy picture of an adhesive includes a large size variation of filler particles. The reflectance (r) of a composite material consisting of two different phases of indices $\rm n_1$ and $\rm n_2$ is given by the equation:

 $r = (n_1-n_2)^2/(n_1+n_2)^2$



Fig. 2. A photograph of the edge of the feet of the lizard gecko, which is able to sustain its weight vertically. Note the dense network of hair, which increase the contact area with the substrate and provide mechanical retention.



Fig. 3. The size of the cutting section of the bur would not be significantly larger than the vertical dimensions of the adhesive to prevent from adverse effects on the free enamel surface during grinding.

and therefore, the deleterious effect of large index differences is well substantiated and should be avoided.

Iron fillers have the advantage of being of the preferred size and, most importantly, can be distributed within the bulk adhesive with a preferred orientation, which would vary among different layers and thus provide optimum mechanical properties to specific loading directions [21]. Moreover, after completion of the adhesive's intended service, alternating-polarity magnets can be used to force the iron fillers to move inside the polymer structure and induce internal cracks. This internal induction of catastrophic failure as a method of facilitating composite debonding can be also achieved with the use of thermally expandable fillers [22]. In this instance, heat can induce an increase in the volume of fillers by 50–100 times, thus causing cracks and fragmentation of the polymerized resin composite.

In addition, research in this field has been directed towards using photooxidation-initiated, hydrolytic, or other forms of degradation to induce a reversal of the adhesive from the crystalline status to the viscous state [23]. However, this method is only available for industrial applications of adhesives, as this mode of debonding is non-compatible with biomedical applications.

The use of thermal treatment on the adhesive could also be applied to achieve a reversal of the condition of the adhesive phase. Glass transition temperature (Tg) in polymers indicates the temperature above which the polymer structure is transformed from the crystalline to the viscous state. In relevant research, 80% of the Tg initiates this transformation to a viscous state. Thus, heating the adhesive could transform it to a paste-like phase which could be removed without any rotary instruments. The problem with this approach lies in the relatively high Tg of currently available adhesives, which range above 100–110 degrees Celsius. Therefore, an 80%-Tg temperature could be well over 80 degrees, which could have adverse effects in the physiology of the pulp.

From the opposite side, a recent approach with conventional adhesives has demonstrated that freezing the bracket-adhesive complex with the use of freezing probe, resulted in an alteration of the remnant adhesive index showing reduced adhesive remaining onto enamel after debonding (Fig. 4).

2.8. Concluding remarks on the application of already existing technological advances on orthodontic materials and processes

The application of many advantageous material applications seems to be impeded by:

 a. lack of an overall knowledge on the level of scientific advances and related armamentaria of materials / tools that could potentially be used to optimize orthodontic materials / processes—as in the case of self-healing polymeric brackets or tribological considerations of metals;



Fig. 4. The post-deboding appearance of enamel with a remnant adhesive of full thickness is an indication of a failed debonding. Ideally a portion of the adhesive, both area- and thickness-wise) should be removed along with the bracket on debonding with a preferred failure pattern being the adhesive cohesive fracture of the composite.

- lack of interest, perhaps due to the projected reduced market share of orthodontic materials, as in the case of self-cleaning brackets, elastomers, or aligners; and
- c. limitations arising from the biomedical character and necessity to apply these materials in the human body, as in the case of photooxidation of composites to facilitate debonding.

2.9. 3D technology and orthodontics

During the last years, digital technology changed the way dentistry and orthodontics is practiced, transforming many of its aspects from analogue to digital. It is not an exaggeration to say that digitization of the oral cavity using 3D scanners is the most important part of this evolution and is responsible for all digital changes that we are observing in the profession. The ability to digitally capture in detail the structures of the oral cavity is the trigger that allows designing and manufacturing of customized appliances. On the other hand, a 3D object without the proper tools to design, edit, and modify the 3D object would be useless. For this reason, computer-aided-designing (CAD) software is an essential tool that can be used to virtually design the orthodontic appliances in a "tailor-made" manner. CAD software has existed for more than 40 years for engineering, aerospace and other fields. In orthodontics, CAD software started to appear at the beginning of our century mainly for handling and creating dental models, or more recently, for the purpose of manufacturing thermoformed clear aligners from manipulated dental models. In the course of time, and as technology was advancing, other software was developed for the designing of more complex appliances such as maxillary expanders, lingual arches, molar-distalizers, etc. The last years, and as new materials appeared in the market, CAD software has been used to design directly printed aligners or even customized brackets manufactured in the orthodontic office, creating a digital selfsufficient environment.

The stage of bringing virtual appliances to real life is called undigitization and refers to the process of transforming a virtual 3D object into a real world object [24]. 3D manufacturing is the actual term pertaining to machines being used to perform this process [25] and is divided into subtractive and additive manufacturing. Subtractive manufacturing is the procedure where material is removed from a mass (disc) to create 3D objects. This procedure is rarely used in orthodontics. On the other hand, additive manufacturing is the process, where an object is developed by laying down successive layers of a material to build up an object. This procedure is commonly called 3D printing and is

used in orthodontics for manufacturing dental models, occlusal splints, metallic appliances, direct printed aligners, brackets etc. Finally, following 3D printing, other machine units are used to clean and completely polymerize the 3D object.

In essence, a fully digital orthodontic office consists of software that gathers and analyses all digital input taken by cone beam computed tomography, an intraoral scanner, if possible, a face scanner, CAD software, and 3D printers. Intraoral and face records are also input into the software to create a "virtual patient" in contrast to the traditional way, where all the records (study models, cephalograms, panoramic radiographs, etc.) cannot be gathered and evaluated as a single patient file [24].

2.10. Orthodontic appliance designing and fabrication

In order to be able to design and manufacture customized orthodontic appliances we need to be able to 3D scan the oral cavity, design the appliance in special CAD software, use a material (resin, slurry, metallic powder, etc.), use a 3D printer to fabricate the object, and finally proceed with the final steps of cleaning, curing, and debonding-sintering. Most of these procedures can be performed in the orthodontic office, while printing metallic appliances (made by Cobalt-Chromium [CoCr], stainless steel, or titanium) can only be performed in special laboratories.

2.10.1. Dental models and aligners

Printing of dental models using special resins is the first digital procedure that was performed in orthodontics by Invisalign (Align Technology, Santa Clara, Calif) at the beginning of our century, while up to that point dental models were only made by pouring plaster into alginate or silicon impressions. The intraoral cavity was digitized using a scanner or by scanning dental impressions and subsequently the 3D dental arches were imported in a CAD software where a setup was performed resulting in exporting multiple dental models. Those models were used to create aligners using the thermoforming procedure, which is not a new technique, but was developed by Sheridan back in the early 90's [26]. Nowadays, the same workflow can be performed in the orthodontic office where thermoformed aligners are manufactured on dental models that are printed following a setup in commercially available CAD software. CAD software can be found online with the option of buying orthodontic cases (according to the number of dental models that are exported) or can be bought and installed in the orthodontic office.

Aligners that would be directly printed without the intermediate step of model-printing and thermoforming have always been in the mind of clinicians and companies (Fig. 5). Nevertheless, the obstacle of creating a proper resin that would adequately create an active appliance could not be easily overcome. Essentially, an aligner is the only customized orthodontic appliance that is printed and directly exerts force to move



Fig. 5. Aligners printed in a vertical orientation. Note the supports that are needed for a successful printing which will be removed in the post printing procedure.

teeth. Anything else is not an active, but rather a passive appliance, which is not meant to move teeth of its own (occlusal splints, metallic appliances, customized brackets). For this reason, a directly printed aligner is an appliance that needs to possess properties, which will enable adequate and efficient tooth movement in the desired direction. On one side, the material properties are limiting the efficacy of the movement, if inadequate, and on the other side the multistep workflow, which is not consistent, creates a non-stable and repeatable environment that might pose threats in the demand to have every time the same aligner quality. Briefly, the workflow of printed aligner manufacturing includes 3D scanning, importing of the scans in a CAD software, where setup and designing of the virtual aligners is performed, 3D printing using aligner resin, removing of the excess resin, and finally post printing curing of the aligners in order to give the aligner its final properties.

The last two years studies have been conducted to investigate many aspects of directly printed aligners. One of the first available resins for printed aligners that appeared in the market was made by Graphy (Seoul, Korea), followed by 3Dresyns (Barcelona, Spain), Luxcreo (Luxmark, Belmont, USA) and Clear A (Senertek, Ismir, Turkey). The first study concerning Graphy's aligner resin investigated the properties of printed aligners aged for one week of use in the mouth of patients [27]. The results showed a non-significant decrease in all the mechanical properties of the aligners at the end of the week. Cytotoxicity and estrogenicity are terms that are discussed in the community when it comes to dental materials and units. In another study, no signs of cytotoxicity and estrogenicity were found in specimens of directly printed aligners [28]. Leaching is similarly an important factor that can lead to problems with the appiance's integrity and also to patient health hazards. In a recent study, urethane was detected in sets of printed aligners [29]—even though the impact of urethane to humans is not precisely known. Nevertheless, since aligners are the only appliances that are renewed every week, possible leaching phenomena of any substance will be kept in constantly high levels in the patient's mouth, thereby creating potential health hazards to the patient. Roughness is another property that should not be overlooked, especially in appliances that are made of polymers. A study comparing Invisalign aligners and directly printed aligners revealed higher roughness values after one week of wearing for the latter [30]. This could lead to easier aligner microfractures, loss of transparency, material leaching, and overall deterioration of their mechanical properties. Nevertheless, the study was done using the initial printed aligner manufacturing workflow and this could have affected the final outcome. A new study with optimized protocols might have shown more favorable results for printed aligners.

Comparison of thermoformed and in-office directly printed aligners in terms of dimensional accuracy revealed higher accuracy for the latter, while there was also a 12% increase of the thickness and significant thickness decrease of thermoformed aligners. Due to the inconsistent multistep procedure, which is prone to errors, a different workflow configuration could present different results [31]. However, in another study, printed aligners were found to apply a constant light force to the teeth owing to their flexibility and viscoelastic properties [32]. The force profile of printed aligners versus thermoformed was also studied from another research team concluding that the forces delivered by printed aligners in the vertical dimension were more consistent and of lower magnitude compared to forces exerted from thermoformed ones [33]. Furthermore, a comparison of the mechanical properties between printed and thermoformed aligners revealed a significant difference in elastic modulus, ultimate tensile strength, and stress relaxation. In addition, moisture of the simulated oral environment showed to have a greater effect on the mechanical properties of the printed aligners compared to the thermoformed ones, and this might affect printed aligners' ability to generate and maintain force levels appropriate for tooth movement throughout their use [34].

Increases in thickness of the directly printed aligners and their effect on tooth movement was investigated in a recent vitro study [35], which

concluded that the ability to change the thickness of printed aligners and the change in force and moments, could be used to optimize the prescribed orthodontic movement while minimizing unwanted tooth movements. This opens new possibilities in the provision completely individualized mechanotherapy for each patient, according to the specific needs of each treatment phase.

As can be shown from the abovementioned studies, each step of the 3D printed aligners workflow, if not performed correctly, could alter the final result. On the other hand, different printers, software, or curing units currently available in the market could have a different effect on the finally printed aligner outcome in terms of their mechanical properties, transparency, leaching, roughness, etc. For this reason, it is essential to investigate what is the effect of using different printers on the final outcome. A recent study comparing the mechanical properties of directly printed aligners using five different 3D printers showed that mechanical properties of 3D-printed orthodontic aligners are directly dependent on the 3D printer used [36].

As is well known, uncured resin (monomer/ oligomer) might exert possibly toxic and allergic side effects on human cells. It is possible that incomplete post-printing cure can increase the chances of toxic or allergic reactions to the patient and therefore, relevant studies on this issue should be carried out before such appliances see widespread use.

Software for direct aligner printing resembles the ones for manufacturing of thermoformed aligners. The only difference is that the operator must design the virtual aligner on the 3D model that will be later printed (Fig. 6). In addition, the operator must define the proper thickness and offset of the aligner, while in Deltaface (Coruo, Limoges, France) software there is an option, where the software detects the tooth movement prescribed in setup and adds more material on the opposite side of the direction of tooth movement (from 0.1 mm to 0.9 mm according to the operator's wish) (Fig. 6). However, the usefulness of this feature in achieving more predictable tooth movement needs to be clinically proven. Artificial intelligence (AI) is another feature that can be incorporated in such software to facilitate faster designing workflow at the steps of teeth segmentation and setup. In addition, a central server, where all the data will be gathered from multiple offices, can be the center where AI analyzes and gives feedback to the orthodontist for future aligner orthodontic treatment. Thus, more accurate and predictable results might be obtained with the help of big data analysis through the use of AI.

2.10.2. Customized metallic appliances

CoCr is an alloy used for decades in dentistry for casting removable or fixed partial dentures. During the last decades, a novel 3D printing technology, called selective laser sintering, was introduced, allowing the 3D printing of various metallic appliances in orthodontics. CoCr alloys are used most of the time, while stainless steel, and titanium ones are

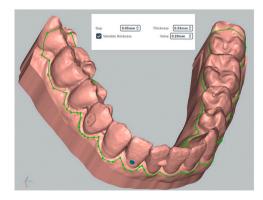


Fig. 6. Printed aligners are easily designed on the virtual model. Deltaface software (Coruo, Limoges, France) offers the ability to increase the aligner thickness on specific areas. This thickness increase is automatically added by the software in places where movement of teeth is detected.

also available but not used that often. Several companies have released in the market machines for metallic printing with different names and technology variations to manufacture metallic objects. However, their big plethora and potentially hazardous materials used in the printing procedure do not allow their installation in the average orthodontic office. The development of this technology allowed the shift from the manual designing and manufacturing of orthodontic appliances to a digital one. Both techniques, analogue and digital, possess advantages and disadvantages which should be taken into consideration when manufacturing orthodontic appliances. Designing orthodontic appliances can be performed using dedicated CAD software such as 3Shape ortho system software (3Shape, Copenhagen, Denmark), OnyxCeph (Chemnitz, Germany), Deltaface (Coruo, Limoges, France), etc. For the skilled designing personnel, professional engineering CAD software (Meshmixer, Blender, etc) can also be used to design appliances. However, the bigger disadvantage of CoCr alloys is the almost complete lack of flexibility of the appliances. 3D-printed bands are rigid compared to commercially-available bands and cannot pass the maximum circumference of the molars, thereby creating retention problems. Several orthodontic appliances can be designed and printed such as maxillaryexpanders, lingual arches, and distalizers (Fig. 7). Nevertheless, many times an orthodontic technician must manually add pre-fabricated parts such as expander-screws, springs, or other parts for molar distalization, because these cannot be printed. The behavior of CoCr alloy was evaluated in a study examining CoCr-based orthodontic appliances placed for 6 months in the oral environment. The results showed that intraoral ageing did not influence the mechanical properties of the appliances, but the appliance showed degradation in the breakdown potential of the protective oxide layer, which results in pitting corrosion. Thus, it is possible that Cobalt may be released in the patient's mouth [37] and this might be potentially detrimental to the patient's health.

2.10.3. Customized orthodontic brackets

After introduction of the original Edgewise appliance by E.H. Angle [38], the development of the straight-wire appliance [39] was in fact the first attempt to create customized orthodontic appliance (even if it was tailored simply to the average patient). A real need for completely customized brackets appeared when lingual orthodontic appliances were introduced, due to the unique nature of the lingual surfaces of the teeth. The following years, customized lingual appliances played a big role in orthodontic treatment, offering adequately predictable results, even for difficult cases.

It wasn't until a few years ago that Ormco (Orange, Calif, USA) created its own series of labial customized brackets, while LightForce (Burlington, Massach, USA) introduced its polycrystalline 3D-printed



Fig. 7. 3D technology enables the orthodontist to design customized orthodontic appliances such as the rapid palatal expansion with anterior hooks for face mask treatment seen in the picture. The material used for 3D printing is mostly CoCr alloy. Nevertheless, not all parts can be printed (i.e. such as the screw) needing the involvement of a dental technician to combine the screw with the printed parts.

customized orthodontic brackets. In both systems a 3D scanning is performed, which is then sent to the company to produce the customized brackets. Such online CAD software enables the orthodontist to create a virtual setup, where customized brackets are designed, approved by the orthodontist, and then printed by the company.

The evolution of 3D-technologies and competition between manufacturers enabled the development of faster, more accurate, and cheaper 3D printers. New materials were invented and introduced to the market, with CAD software being an integral part in the appliances' design. The last years, many orthodontic offices have installed all the necessary units for designing and 3D printing, thus creating small digital laboratories of their own and thermoformed or directly printed aligners, occlusal splints, indirect bonding trays, and dental models are nowadays often manufactured within the orthodontic office.

Nevertheless, orthodontic treatment is mainly based on fixed appliances, the orthodontic brackets, which up to now could not be adequately manufactured in the orthodontic office. 3D technology advancements enable the orthodontic office to become a small lab that can print customized orthodontic brackets. Novel software called Ubrackets (Coruo, Limoges, France) enables the orthodontist to perform a digital setup of imported dental scans and automatically design customized orthodontic brackets together with their customized archwires [24]. The workflow of manufacturing customized brackets can be divided into the designing and the printing part. At the designing part the operator separates the teeth from the gingiva in a stage called segmentation to perform the setup of the dental arches. At the next step the orthodontist chooses to design labial or lingual customized brackets which will be later printed. Following that, the brackets are automatically positioned on a flat rectangular archwire opposite the teeth's surfaces and with special manipulators the operator positions the brackets on the desired place creating customized brackets where their bases are adapted to the tooth surfaces (Fig. 8). The next step is to design indirect bonding trays or positioning keys for each bracket which will help the orthodontist bond them in an accurate way, and which should be easily removed after bonding. Customized archwires can also be exported as 3D files for an archwire bending robot or in a electronic drawing for manual plier bending. Maybe the most important issue to be solved is the material that will be used to create the customized brackets. In the orthodontist's armamentarium several printers can be found together with specialized software to solve the problem of designing and printing. Nevertheless, the key to creating good-quality brackets for orthodontic treatment is the material. Attempts have been made to print customized brackets using hybrid ceramic permanent crown resins (Fig. 9), while the first study to compare two resins, normally used for temporary and permanent crown resins, to print brackets was published a few years ago [40]. The study concluded that there was no significant difference between

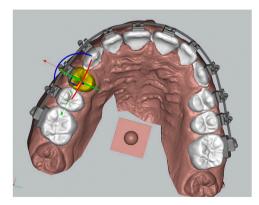


Fig. 8. Ubrackets software (Coruo, Limoges, France) enable the designing and printing customized brackets. The brackets are automatically placed on a flat rectangular virtual archwire opposite their corresponding teeth and can be moved in all directions using a digital manipulator.



Fig. 9. The picture presents the first attempt to print customized brackets using permanent hybrid ceramic crown resin. Positioning keys placed on the teeth cusps and incisal edges were designed in Ubrackets in order to facilitate accurate bonding.

the two resins in terms of mechanical properties. In addition, hardness, a property that is very important for brackets, as it presents the resistance to wear off, was relatively low (though almost double compared to commercial plastic brackets available in the market). In another study, 3D printed zirconia brackets (Fig. 10) made in a ZiproD (AON, Seoul, Korea) zirconia printer were compared to commonly-available Clarity (3 M, Monrovia, USA) and LightForce (Burlington, Massach, USA) brackets [41]. The study revealed high hardness values for Clarity brackets followed by LightForce and zirconia brackets. Despite that, hardness was above the ideal value for brackets making them all suitable for orthodontic treatment. In the same study, zirconia exhibited the higher fracture toughness values followed by Clarity and LightForce. A disadvantage of zirconia brackets was the color, which is white, while a solution to that could be the use of special zirconia paintings that are used to color the brackets the same color with the patient's teeth. Lately, AON (Seoul, Korea) released a translucent zirconia that can be used for brackets printing.

Designing and printing brackets in the orthodontic office is definitely a big step towards creating digital, self-sufficient orthodontic offices. In addition, it seems that the cost of customized brackets is much lower compared to the commercial pre-fabricated ones, while the ability to reprint brackets, in cases of accidental debonds, must not be underestimated. Nevertheless, the advantages of customized brackets are not limited only to the above. Brackets can be designed in bigger mesiodistal widths when great rotations must be corrected or can be smaller when severe crowding does not allow the use of regular sized brackets. In addition, in cases where increased torque must be used when retracting upper incisors, additional torque can be incorporated in the prescription. Overcorrection can be included to the canine brackets to counteract the tipping and rotational side effects movements when they are moved distally into extraction spaces. In the case of customized brackets, no single one prescription exists that will optimally move the teeth in a specific way. On the contrary, the operator must create a unique prescription for each specific patient following existing diagnostics and treatment-plan in a tailor-made fashion. The orthodontist can choose from a big amount of brackets variation to fulfill the orthodontic treatment in an efficient and predictable way.

Lastly, AI is already a reality in our lives and penetrates more and more medicine, dentistry, and orthodontics. In the case of customized brackets, AI can play the role of decreasing the designing time through automation of steps such as teeth segmentation, setup and most important customized brackets designing and positioning [42,43]. A centralized server gathering all data from different offices could use AI analysis to provide feedback for the creation of optimized appliances. AI can be a reliable assistant to our orthodontic treatment, assisting in digital setups, tooth segmentation, predicting teeth movement and growth, tracing cephalograms, etc. Nevertheless, 3D technologies and AI will never substitute the orthodontist but might prove a valuable

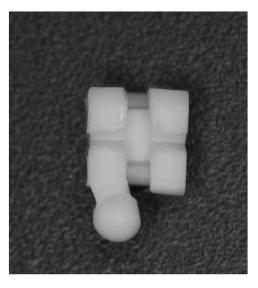


Fig. 10. Zirconia is a material used for dental crown manufacturing using milling technology. A zirconia 3D printer was used for the first time to print customized orthodontic brackets (with a 0.018×0.025 –inch slot). The disadvantage of zirconia is its white color. Nevertheless, new translucent zirconia material has been launched to counteract the current problem.

assistant in our efforts to create better smiles in a more efficient and predictable matter.

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Declaration of Generative AI and AI-assisted technologies in the writing process

None.

Conflict of Interest

TE and SNP have no conflict of interest to declare. NP discloses a financial interest with the company Coruo (Limoges, France) concerning the orthodontic computer-aided design software UBrackets.

References

- Lim KF, Lew KK, Toh SL. Bending stiffness of two aesthetic orthodontic archwires: an in vitro comparative study. Clin Mater 1994;16(2):63–71. https://doi.org/ 10.1016/0267-6605(94)90099-x.
- [2] Lendlein A, Jiang H, Jünger O, Langer R. Light-induced shape-memory polymers. Nature 2005;434(7035):879–82. https://doi.org/10.1038/nature03496.
- [3] Small Iv W, Wilson T, Benett W, Loge J, Maitland D. Laser-activated shape memory polymer intravascular thrombectomy device. Opt Express 2005;13(20):8204–13. https://doi.org/10.1364/opex.13.008204.
- [4] Greiner C, Schäfer M. Bio-inspired scale-like surface textures and their tribological properties. Bioinspir Biomim 2015;10(4):044001. https://doi.org/10.1088/1748-3190/10/4/044001.
- [5] Eliades T, Viazis AD, Lekka M. Failure mode analysis of ceramic brackets bonded to enamel. Am J Orthod Dentofac Orthop 1993;104(1):21–6. https://doi.org/ 10.1016/S0889-5406(08)80120-5.
- [6] Farle A, Boatemaa L, Shen L, Gövert S, Kok JBW, Bosch M, Yoshioka S, van der Zwaag S, Sloof WG. Demonstrating the self-healing behaviour of some selected ceramics under combustion chamber conditions. Smart Mater Struct 2016;25: 084019. https://doi.org/10.1088/0964-1726/25/8/084019.
- [7] Punckt C, Jan L, Jiang P, Frewen TA, Saville DA, Kevrekidis IG, Aksay IA. Autonomous colloidal crystallization in a galvanic microreactor. J Appl Phys 2012; 112:074905. https://doi.org/10.1063/1.4755807.
- [8] Marmur A. The lotus effect: superhydrophobicity and metastability. Langmuir 2004;20(9):3517–9. https://doi.org/10.1021/la036369u.
- [9] Ciasca G, Papi M, Businaro L, Campi G, Ortolani M, Palmieri V, Cedola A, De Ninno A, Gerardino A, Maulucci G. Recent advances in superhydrophobic surfaces

- and their relevance to biology and medicine. Bioinspir Biomim 2016;11:011001. https://doi.org/10.1088/1748-3190/11/1/011001.
- [10] Yin J, Mei ML, Li Q, Xia R, Zhang Z, Chu CH. Self-cleaning and antibiofouling enamel surface by slippery liquid-infused technique. Sci Rep 2016;6:25924. https://doi.org/10.1038/srep25924.
- [11] Sato Y, Miyazawa K, Sato N, Nakano K, Takei Y, Kawai T, Goto S. Study on fabrication of orthodontic brackets with the photocatalytic function of titanium dioxide. Dent Mater J 2009;28(4):388–95. https://doi.org/10.4012/dmj.28.388.
- [12] Baransi K, Dubowski Y, Sabbah I. Synergetic effect between photocatalytic degradation and adsorption processes on the removal of phenolic compounds from olive mill wastewater. Water Res 2012;46(3):789–98. https://doi.org/10.1016/j. waters 2011 11 049
- [13] Ducrot E, Chen Y, Bulters M, Sijbesma RP, Creton C. Toughening elastomers with sacrificial bonds and watching them break. Science 2014;344(6180):186–9. https://doi.org/10.1126/science.1248494.
- [14] Goff J, Sulaiman S, Arkles B, Lewicki JP. Soft materials with recoverable shape factors from extreme distortion states. Adv Mater 2016;28(12):2393–8. https:// doi.org/10.1002/adma.201503320.
- [15] Griffiths JR, Salanitri VR. The strength of spider silk. J Mater Sci 1980;15(2): 491–6. https://doi.org/10.1007/BF02396800.
- [16] Copeland G, Bell BE, Christensen CD, Lewis RV. Development of a process for the spinning of synthetic spider silk. ACS Biomater Sci Eng 2015;1(7):577–84. https:// doi.org/10.1021/acsbiomaterials.5b00092.
- [17] Berengueres J, Saito S, Tadakuma K. Structural properties of a scaled gecko foothair. Bioinspir Biomim 2007;2(1):1–8. https://doi.org/10.1088/1748-3182/2/1/ 001
- [18] Yurdumakan B, Raravikar NR, Ajayan PM, Dhinojwala A. Synthetic gecko foothairs from multiwalled carbon nanotubes. Chem Commun (Camb) 2005;30: 3799–801. https://doi.org/10.1039/b506047h.
- [19] Cristescu R, Mihailescu IN, Stamatin I, Doraiswamy A, Narayan RJ, Westwood G, Wilker JJ, Stafslien S, Chisholm B, Chrisey DB. Thin films of polymer mimics of cross-linking mussel adhesive proteins deposited by matrix assisted pulsed laser evaporation. Appl Surf Sci 2009;255(10):5496–8. https://doi.org/10.1016/j.apsusc.2008.11.012.
- [20] Lee H, Lee BP, Messersmith PB. A reversible wet/dry adhesive inspired by mussels and geckos. Nature 2007;448(7151):338–41. https://doi.org/10.1038/ nature05968
- [21] Erb RM, Libanori R, Rothfuchs N, Studart AR. Composites reinforced in three dimensions by using low magnetic fields. Science 2012;335(6065):199–204. https://doi.org/10.1126/science.1210822.
- [22] Banea MD, da Silva LFM, Campilho RDSG, Sato C. Smart adhesive joints: an overview of recent developments. J Adhes 2014;90(1):16–40. https://doi.org/ 10.1080/00218464.2013.785916.
- [23] Celina M. Review of polymer oxidation and its relationship with materials performance and lifetime prediction. Polym Degrad Stabil 2013;98(12):2419–29. https://doi.org/10.1016/j.polymdegradstab.2013.06.024.
- [24] Panayi NC. DIY Orthodontics: Design it Yourself. Chicago: Quintessence Publishing; 2021.
- [25] Shahrubudin N, Lee TC, Ramlan R. An overview on 3D printing technology: technological, materials, and applications. Procedia Manuf 2019;35:1286–96. https://doi.org/10.1016/j.promfg.2019.06.089.
- [26] Sheridan JJ, LeDoux W, McMinn R. Essix retainers: fabrication and supervision for permanent retention. J Clin Orthod 1993;27(1):37–45.
- [27] Can E, Panayi N, Polychronis G, Papageorgiou SN, Zinelis S, Eliades G, Eliades T. In-house 3D-printed aligners: effect of in vivo ageing on mechanical properties. Eur J Orthod 2022;44(1):51–5. https://doi.org/10.1093/ejo/cjab022.

- [28] Pratsinis H, Papageorgiou SN, Panayi N, Iliadi A, Eliades T, Kletsas D. Cytotoxicity and estrogenicity of a novel 3-dimensional printed orthodontic aligner. Am J Orthod Dentofac Orthop 2022;162(3):e116–22. https://doi.org/10.1186/10.1016/ i.ajodo.2022.06.014.
- [29] Willi A, Patcas R, Zervou SK, Panayi N, Schätzle M, Eliades G, Hiskia A, Eliades T. Leaching from a 3D-printed aligner resin. Eur J Orthod 2023;45(3):244–9. https://doi.org/10.1093/ejo/cjac056.
- [30] Koletsi D, Panayi N, Laspos C, Athanasiou AE, Zinelis S, Eliades T. In vivo aging-induced surface roughness alterations of Invisalign® and 3D-printed aligners. 14653125221145948 J Orthod 2022. https://doi.org/10.1177/ 14653125221145948
- [31] Koenig N, Choi JY, McCray J, Hayes A, Schneider P, Kim KB. Comparison of dimensional accuracy between direct-printed and thermoformed aligners. Korean J Orthod 2022;52(4):249–57. https://doi.org/10.4041/kjod21.269.
- [32] Lee SY, Kim H, Kim HJ, Chung CJ, Choi YJ, Kim SJ, Cha JY. Thermo-mechanical properties of 3D printed photocurable shape memory resin for clear aligners. Sci Rep 2022;12(1):6246. https://doi.org/10.1038/s41598-022-09831-4.
- [33] Hertan E, McCray J, Bankhead B, Kim KB. Force profile assessment of directprinted aligners versus thermoformed aligners and the effects of non-engaged surface patterns. Prog Orthod 2022;23(1):49. https://doi.org/10.1186/s40510-023-00443-2.
- [34] Shirey N, Mendonca G, Groth C, Kim-Berman H. Comparison of mechanical properties of 3-dimensional printed and thermoformed orthodontic aligners. Am J Orthod Dentofac Orthop 2023;163(5):720–8. https://doi.org/10.1016/j. aiodo 2023.13.008
- [35] Grant J, Foley P, Bankhead B, Miranda G, Adel SM, Kim KB. Forces and moments generated by 3D direct printed clear aligners of varying labial and lingual thicknesses during lingual movement of maxillary central incisor: an in vitro study. Prog Orthod 2023;24(1):23. https://doi.org/10.1186/s40510-023-00475-2.
- [36] Zinelis S, Panayi N, Polychronis G, Papageorgiou SN, Eliades T. Comparative analysis of mechanical properties of orthodontic aligners produced by different contemporary 3D printers. Orthod Craniofac Res 2022;25(3):336–41. https://doi. org/10.1111/ocr.12537.
- [37] Zinelis S, Polychronis G, Papadopoulos F, Kokkinos C, Economou A, Panayi N, Papageorgiou SN, Eliades T. Mechanical and electrochemical characterization of 3D printed orthodontic metallic appliances after in vivo ageing. Dent Mater 2022; 38(11):1721–7. https://doi.org/10.1016/j.dental.2022.09.002.
- [38] Angle EH. The latest and best in orthodontic mechanism. Dent Cosm 1929;71: 164–74.
- [39] Andrews LF. The Straight-Wire Appliance: Syllabus of Philosophy and Techniques. Rev. ed. San Diego: University of Michigan publications,; 1975.
- [40] Papageorgiou SN, Polychronis G, Panayi N, Zinelis S, Eliades T. New aesthetic inhouse 3D-printed brackets: proof of concept and fundamental mechanical properties. Prog Orthod 2022;23(1):6. https://doi.org/10.1186/s40510-022-00400-z
- [41] Polychronis G, Papageorgiou SN, Riollo CS, Panayi N, Zinelis S, Eliades T. Fracture toughness and hardness of in-office, 3D-printed ceramic brackets. Orthod Craniofac Res 2023;26(3):476–80. https://doi.org/10.1111/ocr.12632.
- [42] Hao J, Liao W, Zhang YL, Peng J, Zhao Z, Chen Z, Zhou BW, Feng Y, Fang B, Liu ZZ, Zhao ZH. Toward clinically applicable 3-dimensional tooth segmentation via deep learning. J Dent Res 2022;101(3):304–11. https://doi.org/10.1177/00220345211040459.
- [43] Schneider L, Arsiwala-Scheppach L, Krois J, Meyer-Lueckel H, Bressem KK, Niehues SM, Schwendicke F. Benchmarking deep learning models for tooth structure segmentation. J Dent Res 2022;101(11):1343–9. https://doi.org/ 10.1177/00220345221100169.