Dental Implants are an increasingly popular solution for edentulous people with impaired masticatory functions while satisfying cosmetic requirements. It is estimated that over three million patients have been treated in the USA alone, with 500,000 implants placed annually. The implant is an engineered structure aimed at restoring normal masticatory performance and efficiency while being compatible with the living tissues. Therefore, the subject of implant dentistry belongs apparently first and foremost to clinical dentistry, judging from the vast body of literature published each month in dentistry journals on topics related to biological reaction around the implants [1]. With that, implant design and mechanical performance are essentially the realm of materials, mechanical and biomechanical engineering. In other words, Clinical Dentistry and Engineering are two complementary disciplines that should combine to tackle complex problems of the engineering structure in its living environment.

Consequently, this paper, which could have been entitled “The Engineer’s journey into Implant Dentistry”, will survey some of the recent engineering developments and their contribution to the improvement, or at least understanding, of the implant’s functionality. We will deliberately set aside those many clinical and biological considerations, which despite their huge importance, cannot be directly related, as of yet, to engineering developments in the authors’ opinion.

The paper is divided into three main parts, namely the implant itself, the bone system (succinctly), and finally the bone-implant system and its interactions.
It is important to emphasize that we present here an engineering perspective, which is necessarily simplified with respect to the complex bio-reality, as the design of engineering systems implies certain simplifications, assumptions, and parameter lumping so that a first solution can be proposed.

The Key Actors

The Dental Implant

Material and Implant Geometry

Since the implant is to be inserted into the jawbone of the patient, a first concern is that of its biocompatibility in order to minimize any potential adverse reaction from the surrounding tissues. In that respect, commercially pure titanium (CP-Ti grade 4), and its high strength alloy Ti6Al4V (grade 5 or grade 23) are currently the most popular materials for implant manufacturing [2], although some concerns exist about the innocuity of titanium to the surrounding tissue, even if there is no absolute consensus on that issue [3–6, 7••]. This issue will appear again in the context of long-term reliability of dental implants.

Mechanically speaking, dental implant metals such as titanium and alloys, are all tough and ductile. This implies that they are easily machined, and resist cracking while dissipating mechanical energy through permanent plastic deformation.

Another category of materials considered in implant dentistry is that of the ceramic materials, such as zirconia [8, 9, 10••]. Those are very hard materials with superior elastic characteristics with respect to metals. Ceramics are also characterized by their low resistance to fracture (referred to as “fracture toughness” [11]) and lack of plastic deformability, which makes them virtually non-machinable at room temperature. Unlike metals, ceramics perform poorly under tensile loading, as opposed to compression. Likewise, due to their very limited ductility, those materials are not aimed at sustaining shearing loads.

If one were to further compare the mechanical behavior of metals to ceramics with respect to fracture, one could claim that whereas metals are “defect tolerant” to a large extent, ceramics have almost “zero tolerance” for defects [12••]. Defect here is to be understood in the broadest sense as present in the base material, or caused by machining or service. Translating the concept of a high fracture toughness into practical terms, the presence of a micro-crack in a metal does not mean immediate fracture, allowing for delayed crack growth by fatigue, to be discussed later. By contrast, a micro-crack in a ceramic structure has a high probability of immediate propagation leading to final fracture under low applied stresses. As a more general note, ceramics are rarely employed as structural materials for those reasons, while their optical, chemical inertness and electrical properties make them quite attractive for other applications. However, the quest for strength coupled to cosmetic considerations, at the expense of toughness, have made ceramic materials as a candidate for implant dentistry.

Over the years implant design has gone through major geometrical changes. Four main types of dental implant designs that have been developed and used in clinical dentistry, including a subperiosteal form, blade form, ramus frame, and endosseous form [13].

Endosseous dental implants are typically screw-shaped, inserted into either the maxilla or mandible, and act as a replacement for the tooth root. There are three major macro-design types. Screw threads, solid body press-fit designs (cylindrical, conical), and/or porous-coated designs. All macro-design types affect widely the short- and long-term implant stability, and determine success or failure of the implant.

Most implants today are screw type implants, either monolithic or comprised of two or more parts, namely the intrabony structure called the implant body, and the suprastructure (single or multiunit abutment), connected together by a single or several screws. Each manufacturer has its proprietary design regarding the specific thread, implant diameter, length, and general shape (conical) type of implant (abutment connections), which all contribute to the biological tissue reaction, ease of insertion and stability in the jawbone. One can find in the market countless different dental implant configurations.

From an engineering perspective, one cannot use blindly the concept of optimal design for a dental implant, unless the term “optimal” has been formally defined. To perform structural optimization, a goal must be clearly identified, such as reducing the stress level at the bone-implant interface, optimizing the mechanical long-term performance of the implant or other. The complexity here is that the implant cannot be considered as a standalone structure, but its environment and the interaction between the two must also be accounted for. Here, what would be a goal for optimization can sometimes lead to unwanted consequences on the other hand. A good example would be that of “stress shielding”, which will only be mentioned here, as it links the elasticity of the implant to the stress (or strain [14]) level endured by the bone, raising some concerns as to the mechanical suitability of ceramic materials as implant materials. Structural optimization means that once a goal is identified, the design will be engineered such as to reach or come close as much as possible to the goal.

To summarize that section, one cannot really invoke an “optimally designed” dental implant in the broadest context, but one can certainly outline its specific advantage in a well-defined domain.

Applied Loads and Strength Consideration

Being a mechanical structure, the implant has to withstand mastication loads. However, while the frequency of mastication loads is relatively well defined, the amplitude of these
loads can be extremely variable, depending of course on the subject, type of food consumed, and implant placement in the oral cavity. The total loading duration for teeth/implants is about 30 min daily [13, 15]. The frequency at which the loading is applied ranges from 48 to 112 cycles/min [16]. As of today, one can find a very wide range of reported load values, ranging from a few tens of N to almost 2000 N, as noted in [17]. While such a breadth of values may be the result of the measurement procedures, one cannot really define a standard load for design purposes, or rely on the concept of a characteristic load.

With respect to the above, the design of a dental implant is driven by two considerations: Static strength and long-term performance (fatigue). Therefore, the “state of the art” procedure, recommended by ISO 14801 standard [18], consists of loading monotonically an implant until noticeable irreversible (plastic) deformation or fracture is experienced, thereby defining the ultimate load-bearing capacity of the structure. Here, the load is applied at a typical angle of 30° with respect to the implant, such as to mimic some “worst case” intraoral situation of a slanted tooth. As a result, most of the published work on implant strength adopts this angular value for implant stress calculations. While masticatory load values are quite variable, as mentioned above, it can be noted that as long as the structure remains linearly elastic, the linearity of the problem alleviates this apparent limitation. In other words, calculated stresses and strains corresponding to an applied load of 1 N will be multiplied by 10 for a load of 10 N.

In parallel, the constant quest for stronger materials motivates research in the field of dental implants. Setting aside the abovementioned high-strength ceramics, the limited choice of implant materials has been recently expanded by what is called “severe plastic deformation”, SPD [19]. In this process, a conventional metal is severely deformed to very large strains until its initial grain microstructure is destroyed and replaced by much smaller nanograins, thereby causing its strengthening due to the well-known Hall-Petch effect [11]. Here, significant increases in strength have been recently reported [19, 20] which could in principle bring about to a reduction of the characteristic implant dimensions without reducing or compromising on the applied loads. It is expected that additional work on SPD in dental materials will appear in the near future to confirm and expand this promising route.

Long-Term Mechanical Survival

Although considered as a rare complication [21, 22, 23], implant fracture occurs in its bulk, or more frequently in the connecting screw [24]. Since this event takes time to occur, implant fracture is due to what is known as metal fatigue, a time-dependent failure mechanism. Metal fatigue, by its very definition, results from repeated loading, which should not be confused with the particular case of periodic loading. While long suspected, implant fatigue fracture has only been recently identified through a meticulous series of fracture surface characterizations of both lab-fractured and in vivo collected implants. The failure analysis process established beyond any doubt the operation of metal fatigue as the main fracture mechanism of the implant [25]. Here, it is interesting to note that the subject of fatigue, which is of prime concern in any engineering structure (bridge, aircraft, automobile, etc.), has been relatively set aside in implant dentistry. This may be the result of the small (reported) incidence of implants’ fracture, or simply that of the more common biological complications that bring about to early implant extraction well before any mechanical failure can occur.

A central concept is that of the “fatigue limit”, namely the value of the load that, cyclically applied, will not cause fracture of the implant after a given period (typically five million cycles). Here, the prevailing paradigm is that as long as such load levels are not exceeded, the structure remains structurally sound. The traditional way of determining this limit, namely the S/N (load-cycles to failure) curve [26] requires a rather large sample size, long-testing time, and associated costs [17]. Therefore, the recent years have witnessed the development of accelerated test methods, the goal of which is not the determination of the S/N curve in its entirety, but rather the identification of the fatigue limit [27, 28]. From the ISO standard point of view [18], the fatigue limit is the parameter to be measured and reported.

The obvious question that arises is whether the designer and the patient can make sure this limit is never exceeded. Given the reported variations in applied loading configurations, this point is highly debatable [29].

Titanium and alloys are generally regarded as materials that possess a high resistance to fatigue crack initiation. Regarding the abovementioned SPD processing, while the latter definitely improves the strength of the implant material, it remains to be shown beyond any doubt that the fatigue characteristics of those materials is equally improved. Preliminary results seem to indicate that this is the case [20], but the reported trend needs to be firmly confirmed before any application, noting in passing that this process and the associated machining may increase the production costs of the implants. It is also important to note that there is no known relationship between a material’s strength and its fatigue performance, so that even if the only improvement due to SPD is the material’s strength.
without fatigue behavior, this will nevertheless be deemed to be an important progress in implant engineering, as it will allow to reliably develop smaller size (narrower) implants. By contrast, the fatigue performance of engineering ceramics is less clearly defined, since once a microcrack has formed, it is likely to propagate rapidly without any intermediate stable growth phase like in a metal. To this, one must add that tensile fatigue of ceramics is quite difficult to investigate because of the low toughness of those materials, as discussed earlier. Steady fatigue crack propagation is very difficult to observe experimentally for those materials subjected to conventional fatigue testing [30].

In any case, the designer needs to estimate the actual duration of service of the dental implant. Noting that this problem encompasses all engineering structures, one can find in modern design tools, such as finite element [31] codes, including special routines that estimate the fatigue life of a component. Here, fatigue engineering is somewhat limited in the sense that the most popular way to do so is to rely on the so-called Palmgren-Miner cumulative damage rule despite its obvious limitations [26••, 27]. Dental implants are no exception and they can be evaluated using this procedure, as found in several papers on fatigue life predictions (see e.g. [32]).

A radically different approach was recently proposed regarding long-term performance assessment of dental implants. Assuming that an implant will fracture sooner or later in service, along with the inherent uncertainty on the applied loads and their frequency, not to mention the ambient environment, the alternative approach consists of testing the implant under random spectrum loading conditions. Those conditions, which are the random version of a functional spectrum (e.g., daily mastication spectrum) simply consist of the application or random loads that vary both in frequency and in magnitude within prescribed limits. While such a spectrum is not deemed to reflect realistic “average” mastication (since there is no such thing), the use of one spectrum and its application to any kind of geometry, material and environment yields a value of the time to failure. The mere comparison of the times to failure of each tested configuration will yield the figure of merit of the configuration in question. As such, that random spectrum approach is a first attempt to evaluate the functional performance of an implant, instead of its limit state. In other words, this method allows for a direct and reliable comparison of implants, would it only be to evaluate the effect of design modifications on the mechanical fatigue performances.

Aside from the mechanical considerations, it is important to know that the intraoral environment is highly variable and definitely not “neutral” to metallic implants. Without getting deeply into details, two potential failure mechanisms are to be suspected, in addition to the repeated type of loading, and those are corrosion and stress corrosion, respectively [3, 4, 6, 33, 34]. While corrosion simply implies a chemical attack mechanism, stress corrosion refers to the joint synergistic of corrosion and stresses, when the former is accelerated by the latter. Judging from the large body of literature available (some of which cited above), one can understand that the subject is of prime importance. Yet, titanium and its alloys are considered to be quite resistant to corrosion in bodily fluids, but no firm conclusion seems to be available to date, in view of the vast span of chemical compositions found in those fluids [35••]. One can tentatively consider the pH of the solution as the main characteristic of the fluid, but this might be too restrictive. Here, one should remark that firm evidence of pitting corrosion operation, for instance, is still missing, and the simple reason might be that the rough nature of the implants’ surface makes it difficult to distinguish a corrosion pit from natural roughness. Another related point is that of the exact action of the corrosive medium: does it accelerate crack formation, or crack propagation or perhaps both? Regarding crack propagation, the literature contains ample information on so-called Paris plots (cyclic crack growth rate [26••], that can clearly reveal any corrosive influence on crack propagation. Concerning crack initiation, the problem is more subtle and not fully solved to date. Let us note here that the indirect consequence of a corrosive attack will be the release of metallic ions to the surrounding bone tissue. A review on the subject can be found, e.g., in [5], but additional research is definitely needed. As of today, one can find studies focused on a specific medium, such as artificial saliva, fluoride or simply saline solution, as e.g. in [36, 37], or even using cell culture, as in [38]. It is interesting to note that in [36], fractographic information was used to draw conclusions about the influence of a potentially corrosive medium on the average fatigue crack growth rate, for a dental implant subjected to random spectrum loading. It seems like in this specific subject, chemistry, materials science, biology and clinical dentistry could join in a mutual effort to clarify the general situation.

The Implant Surface Condition

It has long been recognized, since the inception of the osseointegration concept [39], that the surface of a dental implant must exhibit a certain degree of roughness in order to facilitate an improved and faster attachment to the bone. While many estimates of surface roughness have been defined in the field of tribology (see e.g. [40••]), the most popular one in the field of implant dentistry remains the so-called surface roughness Ra (linear) or its areal variant, Sa. In that respect, the authors are not aware of recent studies aimed at the identification of the most relevant surface roughness characterization parameter besides Ra/Sa (see e.g. [41–44]).

To achieve a given degree of surface roughness, many surface treatments have been devised which can either consist of a surface deposit using e.g., plasma spray, or simply result from spraying small hard particles, similar to shot-peening, followed by acidic etching for additional roughness and
possibly removal of particle residues [13]. Another treatment is based on water jet blasting [45]. As of today, the most popular treatment is the so-called “grit-blasting and etching” process. While this process is convenient and easy to apply, it is only recently that questions have been raised as to its mechanical benefits, as opposed or complementary to its osseointegration ones [46]. Namely, it has long been known that the hard ceramic particles are likely to remain embedded on the implant surface, sometimes covering 7% of its area, as reported in [47]. Aside from potential biological issues, the mechanical failure of dental implants was shown to be sometimes the direct consequence of particle embedment that cannot be reversed by chemical post-treatments. Such particles can generate micro-cracks which act as embryos for future fatigue cracks [25•, 46]. This point deserves additional attention and research effort.

Here, one cannot overlook modern and recent production techniques grouped under the generic name of 3D printing (laser additive manufacturing or electron beam) which have successfully produced a wealth of Ti alloy structures, including dental implants. While the subject is constantly developing, it is now established that in terms of mechanical properties, the printed Ti alloy is superior to its conventionally machined counterpart [48], while its fatigue response remains to be characterized. An interesting byproduct of this production technique is the relatively rough surface state of the printed structure which usually requires a “final touch” by conventional machining, while in the current context this might be a definite advantage of the finished product. This point is not yet widely investigated but will surely be in the near future.

Regardless of the roughening technique, the current range of attainable surface roughness is quite narrow, so that the relative benefits related to rougher implant surfaces are not fully characterized, which is one of the conclusions of a recent systematic review on the subject [49].

Having surveyed some of the key issues in the purely mechanical aspects of dental implants, we will now turn our attention to the bone system, again with emphasis on the main parameters that are needed to comprehend the bone-implant system interaction.

The Bone

The jawbone is comprised of two macrostructures, namely the hard (cortical) bone and the softer (filler) trabecular bone, of a cellular structure [50••]. The following characteristics are essential for optimal modeling of any mechanical process applied to the bone.

Due to the microstructure of the cortical bone, comprised of directional osteons, it is more realistic to assign anisotropic material properties to it, namely orthotropic, especially in the mandible, as shown experimentally on cortical bone samples [51–53]. Moreover, in the case of the mandible, those properties are spatially heterogeneous.

The same applies to the trabecular bone due to its microstructure being comprised of a net of very porous trabeculates. Here too, the resulting mechanical properties are anisotropic [54, 55], and it is hard to relate the microstructural properties to the macromechanical properties. Moreover, experiments are difficult to conduct, due to the high porosity and the possibility of local failure in the sample. Yet there are some works that managed to overcome those issues, and measured the mechanical properties in one or 2 directions, eventually assigning the trabecular bone isotropic properties [56–58].

In view of the above, the assumption of isotropic bone mechanical properties could be considered as a first approximation, because of a gap of knowledge for anisotropic mechanical constitutive models, for example when bone plasticity or viscoelasticity/viscoplasticity are considered.

The next matter that requires consideration is that of the constitutive model for both cortical and trabecular bones, i.e., the stress-strain relationship, when the simplest one is to assign linear elastic properties (eventually anisotropic) as e.g., in [59, 60]. Yet, one can find much more elaborate constitutive models, that take into account bone yielding, plasticity, viscoelasticity, and viscoplasticity [61–64, 65••, 66–68]. Note here that the bone behaves differently under compression and tension, not to mention shear, as expected from a porous structure. This has been taken account in some of the examples given before for constitutive models. For example, in [64] a constitutive model based on experimental studies for bovine cortical bone tissue was presented. The model depicted viscoelastic effects, i.e. hysteresis, stress relaxation and rate-dependence, with good agreement to the experiments. In [62], an elasto-viscoplastic constitutive model was introduced, which depicted the behavior of the material beyond yield, including softening. This model was then compared to compression experiments of bone samples with good agreement.

Another central issue is that of bone failure. Here, the very definition of failure is crucial, as bone yielding could be considered as one type of failure. One must select whether to formulate yielding in terms of a stress-based criterion [69, 70] or critical strain levels [69, 71, 72], or combined in terms of strain energy density.

Finally, if failure amounts to fracture, bone damage must be considered and modeled in terms of evolution. Recent work by [65••], has proposed a model that depicts damage accumulation and evolution in the cortical bone. The model produced the key macroscopic features of bone tissue damage, with remarkable agreement with the experiments it was based on.

The Bone-Implant System

Having defined the components of the system, the main issue of interest is that of their interaction. Since the implant itself
has been extensively studied and modeled, as discussed earlier, the emphasis should be put on the bone-implant interaction, as seen from the bone side. In other words, the implant is meant to apply boundary conditions on the bone, causing it to undergo stresses and strains, that might lead to its remodeling (including dissolution or growth), and eventually fracture. In such an interaction, it is evident that the abovementioned issues about bone modeling are of prime importance to well define the problem at hand.

Another critical point is that of the representation of the bone-implant interface. Should it be modeled using extensive microstructural detail, as available through modern imaging techniques, or rather “lumped” into a coefficient of friction that could evolve with progressing osseointegration? As of today, one still finds many numerical models in which the bone and the implant are perfectly bonded, which is an idealization of perfect osseointegration, whereas the reality may be more nuanced, consisting of a variable percentage of bonded bone, the rest being frictional [73].

Moreover, given that the bone is a living structure that reacts to mechanical stimuli, this point should be taken into account if the prediction of the bone state is to be accurate [74, 75].

A central paradigm, called the “mechanostat model” [76] states that there are ranges of strain (not stress) that may cause bone dissolution when they are low and the bone is not solicited, normal operation and regrowth or eventually failure/fracture. The model does not address the kinetics of either process but rather their qualitative occurrence. While the notion of strain may seem somewhat imprecise, recent work by Piccinini et al. [77] has identified the equivalent (octahedral) shear strain as the relevant strain parameter, noting in passing that the underlying assumption is that of an isotropic bone model.

At this stage, given the complexity of the problem that cannot simply be tackled by analytical approaches, the main modeling tool is numerical, more specifically the finite element method (FEM). While it could be thought that FEM analysis is often viewed as the ultimate modeling tool, it is recommended to keep in mind that the results of an FE analysis are as good as the physics input in the problem through the proper selection of material models, interaction, and boundary conditions. Most of all, the reader should be made aware that unphysical models will also yield “results” with an FE analysis so that validation is needed to confer credibility to the results [70]. Yet, validation, e.g., through comparison with experimental results, is not always possible due to the inherent experimental complexity and ethical dilemma of biomechanical experiments, and in that case, the FE analysis can be used to probe the sensitivity of the calculated results to variations in the input parameters. Such analyses will definitely provide indications as to the relative importance of each parameter.

Here, one can distinguish two basic approaches. The first, more recent, which is increasingly gaining momentum, consists of analyzing detailed (and very large) numerical models based on fine microstructural characterization provided, e.g., by micro-CT or CBCT [78, 79]. The second, more classical, consists of analyzing a geometrical model, sometimes simplified.

Vanegas et al. [80] proposed a sophisticated mathematical model for bone osseointegration. The model is quite elaborate, but the authors claim it reproduces several physical/clinical features of the osseointegration process although experimental validation is not included. Damage and failure of the trabecular bone were studied based on micro-CT models by Harrison et al. [81]. This work outlined the importance of both the model and experimental resolution to pinpoint fine features of the bone failure. A micromechanical model for bone fracture at the osteon level was reported by Giner et al. [82]. No attempt was made to extend the presented results to the more macroscopic bone scale. A relatively recent review of the “high resolution” modeling techniques can be found in [83], although this field is constantly expanding alongside with the computing power so that new developments are expected, as in [84].

However, one may wonder if and how such studies can be integrated at the more “engineering design” level of dental implants, and here, it seems like the more classical “continuum approach” has its potential.

In that context, the emphasis is on more “macroscopic”, daily clinical procedures such as bone drilling [85, 86], or implant insertion, in relation to the insertion torque for instance. Dorogoy et al. [87] recently modeled the insertion process of a commercial implant in the jawbone, reporting the evolution of the applied torque in relation with the mechanical characteristics of the bone. Such studies, while lacking the high resolution of the previous studies, are nevertheless attractive for the engineering design of the implant and insertion procedure, based on the individual bone characteristics of the patient, or in comparison with experimental testing, as in Duyck et al. [88].

Here, one might venture into a comparison with the realm of solid mechanics and the so-called quasi-continuum method [89] in which one starts with a “coarse” finite element calculation that is seamlessly refined down to the atomic scale, when there is a need for that, such as the presence of a crack (singularity) in the structure. One can therefore assume that future developments in the computational field will increasingly strive at developing the so-called “micro to macro” approaches, which will blend together information obtained and modeled at the microscopic scale together with that obtained through conventional finite element simulations.

A last point which will not be developed here for the sake of brevity is that of the coupling between the mechanical calculations and the biological reaction at the bone level. As mentioned earlier, simple models such as the mechanostat [90] can be successfully implemented into numerical simulations to represent the bone evolution with time, for instance. As of today, such attempts exist, which can be quite complex,
but may indeed benefit in the future from the high resolution observations, bringing them to the more applied side of Engineering Dentistry, as e.g. in [42, 73, 77, 91–93].

Finally, two seemingly important points deserve further attention.

The first concerns testing and modeling of actual intraoral loads, with their effects on both the mechanical (fatigue) performance of the implant but also on the evolution of the host bone. This goes way beyond the current flurry of partial S-N curves published every year.

Next, it is important to realize that the engineering concept of “model reduction” applies to dentistry as well. Namely, while the real picture can be extremely complex and rich in details, progress can only be achieved when the salient and most influential features of the problem are clearly identified without attempting to model each and every point in detail. More specifically, it is the authors’ opinion that a tractable model of the bone-implant interface, in which mechanical, biological, and chemical concepts are embodied and coupled is still missing.

With such a model, past a preliminary assessment of bone stresses and strains for instance, the actual performance of the implant and the evolution of its bony environment can be reliably modeled to predict the long-term success of the implant.

Concluding Remarks

We have tried to survey what we consider to be the actual and relevant issues of dental implant engineering, with emphasis on the implant design, materials, and interaction with the living bone as viewed from the modeling perspective. Throughout the review, we have emphasized research directions and developments blending together fundamental and applied science, pointing out to future directions worth being developed.

The main conclusion of this brief survey is that Clinical and Engineering Implant Dentistry are two complementary disciplines, and it is precisely this complementarity that will bring about to new developments in the field. Clinically informed modeling will shed light on and also help focus clinical work. In parallel to technological advances in clinical diagnostic and implant fabrication processes, one can expect that in the near future, the combination of engineering models and clinical characterization will bring about to the development of personalized implant dentistry.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, recently published, have been highlighted as:

- Of importance
- Of major importance


