SYMPOSIUM INTRODUCTION

The Integrative Biology of Gecko Adhesion: Historical Review, Current Understanding, and Grand Challenges

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Synopsis Geckos are remarkable in their ability to reversibly adhere to smooth vertical, and even inverted surfaces. However, unraveling the precise mechanisms by which geckos do this has been a long process, involving various approaches over the last two centuries. Our understanding of the principles by which gecko adhesion operates has advanced rapidly over the past 20 years and, with this knowledge, material scientists have attempted to mimic the system to create artificial adhesives. From a biological perspective, recent studies have examined the diversity in morphology, performance, and real-world use of the adhesive apparatus. However, the lack of multidisciplinarity is likely a key roadblock to gaining new insights. Our goals in this paper are to 1) present a historical review of gecko adhesion research, 2) discuss the mechanisms and morphology of the adhesive apparatus, 3) discuss the origin and performance of the system in real-world contexts, 4) discuss advancement in bio-inspired design, and 5) present grand challenges in gecko adhesion research. To continue to improve our understanding, and to more effectively employ the principles of gecko adhesion for human applications, greater intensity and scope of interdisciplinary research are necessary.

Introduction

Although referring to issues related to public health and insect control, rather than adhesive capabilities, Loveridge (1947) noted that, "It is probable that we are only on the threshold of discovering the importance of geckos to mankind." Since the turn of the millennium there has been an explosion of interest in them from not only biologists but also physicists, chemists, computer scientists, engineers, materials scientists, and biomimeticists, triggered by the elucidation of the mechanism (Autumn et al. 2000), at the molecular level, that permits geckos to stick to surfaces. This discovery was pivotal in bridging the gap between assessing the adhesive capabilities of the entire adhesive apparatus in the intact, living animal and obtaining empirical evidence about the adhesive capabilities of the individual agents of adhesion—the setae.

Recent breakthroughs have resulted from approaches applying nanotechnological techniques to explore phenomena that were previously largely intractable. Endeavors to duplicate the adhesive capabilities of geckos (Russell and Johnson 2009), a phenomenon that arose at least 100 million years ago (Bauer et al. 2005; Arnold and Poinar 2008; Daza et al. 2016; Fontanarrosa et al. 2018), requires an understanding of the way in which geckos develop, grow, and deploy their adhesive structures. Over the past 20 years a modest degree of reciprocity has occurred between pure and applied research as they relate to this issue, but increased interdisciplinarity is needed to attack crucial issues and maintain progress.

Geckos are relatively large animals (body mass range 0.2–200 g) that can temporarily and reversibly adhere to substrata ranging from the molecularly smooth (Autumn et al. 2000) to the macroscopically very rough and undulant (Russell and Johnson 2007), employing microscopic integumentary

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outgrowths on the ventral surface of the digits (Fig. 1A) (Russell 1979) as well as, in some species, the tail tip (Vitt and Ballinger 1982; Bauer 1998; Alibardi and Bonfitto 2019). The evolutionary precursors of adhesive setae were small spinules, carried on friction plates on the subdigital (and subcaudal) surfaces (Peattie 2008; Russell et al. 2015), that enhanced traction by increasing frictional interactions.

Attachment can be established and broken repeatedly within milliseconds (Russell 1975, 2002), apparently with little wear occurring (Autumn et al. 2014) between the monthly or longer intervals (Maderson et al. 1970) between skin shedding bouts. The integumentary outgrowths are arranged in orderly, structured, and intricately-patterned fields (Johnson and Russell 2009) (Fig. 1B) and strong attachment forces are created by the setae, which are directional, self-cleaning (Hansen and Autumn 2005), and controlled by a hierarchy of linked anatomical components (Figs. 1B and 2 A–C), permitting seemingly instantaneous adjustment to local circumstance (Russell 2002).

Setae exhibit a wide array of structural variation of expression, not only between different species of gecko (and other lizards, such as anoline polychrotids that also exhibit similar modifications), but also along the digits of a single individual (Fig. 1B, C) (Russell et al. 2007; Johnson and Russell 2009). Even for a single species there is no such entity as a typical seta, and their form and structure varies in subtle ways from region to region (Johnson and Russell 2009). Extremely close contact between the organism and the substratum is via the finely subdivided setal tips. Investigations of the collective functional attributes of setae have largely focused on extrapolations from generalizations about the form and function of "typical" individual setae, and much has been deduced from this. For practical and dynamic mimetic applications of gekkotan adhesive principles, however, it is likely that a deeper understanding of the local regional variation of structure of the setae, their geometric patterning into fields (Fig. 1B), and their underlying control mechanisms will result in the development of more effective models.

Determining how attachment is achieved

Pioneering work attempting to address how attachment is brought about in geckos stretches back to the beginning of the 19th century (Home 1816a, 1816b). The ability to test the ideas being advocated, however, has often lagged behind explanatory theory,
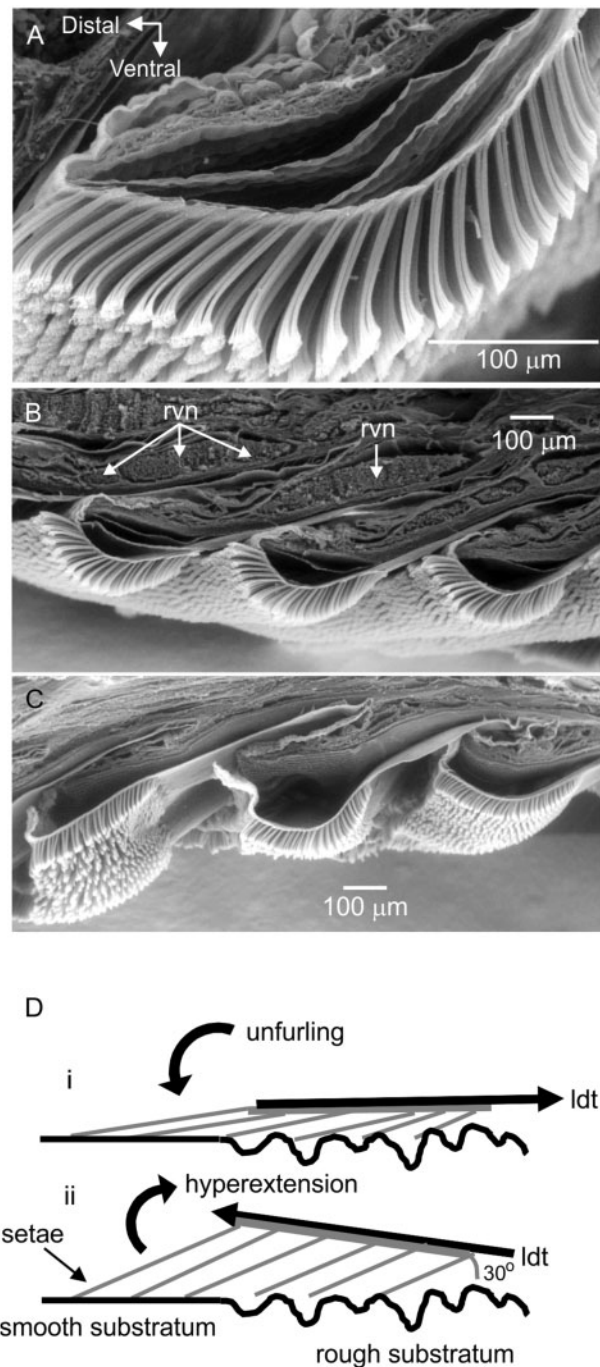
Fig. 1 Setal field morphology of the Tokay gecko (*Gekko gecko*). **A**. Scanning electron micrograph (SEM) of a distal scansor in longitudinal section. Multiply-branched, canted setae arranged in tetrads are aligned in rows along the proximodistal length of the scansor, and in ranks across its mediolateral width. The setae diminish in length toward the proximal end of the scansor. The orientation arrows depicting distal and ventral apply to all four panels in this figure. **B**. SEM of a series of three scansors at a more proximal location on the toe pad to that depicted in panel A. The setae of each scansor are continuous with those of its anterior and posterior neighbors, making up a unified field of setae along the proximodistal extent of the toe pad. Branches of the reticular vascular network (rvn) are evident in the proximal

largely due to a lack of appropriate technology allowing investigation at the necessary scale.

The morphology of subdigital setae was revealed via macroscopic and light-microscopic observation (Home 1816a; Cartier 1872), as was setal branching (Schmidt 1905). Electron microscopy revealed more detail of their structure, geometry, and interspecific variation (Altevogt 1954; Ruibal and Ernst 1965; Peterson 1983), and led to proposals of various hypotheses about attachment as an interaction between surfaces.

Early theories postulated attachment via sticky secretions but were quickly refuted because of an absence of appropriate glands (Cartier 1872). Suction was suggested (Home 1816a; Wagler 1830; Simmermacher 1884; Gadow 1901; Kunitzky 1903), but soon refuted experimentally (Weitlaner 1902; Dellit 1934). Electrostatic attraction was advocated (Schmidt 1905), but was criticized (Hora 1923), and experimentally refuted (Dellit 1934), at least as a major mechanism of attachment, even though allowance was made for it to possibly be supplementary to other mechanisms (Maderson 1964; Hiller 1968). The suggestion that setae have a very high coefficient of friction (Hora 1923) led to the hypothesis that geckos attach by way of frictional forces, and this idea remained dominant for many years (Dellit 1934, 1949). Mahendra (1941) visualized setae

as structures capable of microinterlocking with substrate asperities, but this was rejected (Maderson 1964) on structural grounds and later by the demonstration that gecko adhesion can occur on molecularly smooth surfaces (Autumn et al. 2000).

The application of scanning electron microscopic techniques to investigation of setal morphology (Ruibal and Ernst 1965; Hiller 1968, 1976) led Hiller (1968) to re-examine the possibility that intermolecular forces, or true "adhesive" forces, are responsible for attachment in geckos, as originally suggested by Haase (1900). Hiller's (1968, 1969) experiments revealed that a gecko's ability to adhere is directly related to the surface energy of the substrate, as measured by its water contact angle. Setae were determined to be able to stick to hydrophilic surfaces (those with a low water contact angle) but to be less capable of adhering to hydrophobic surfaces (those with a high water contact angle), suggesting that the adhesive force generated by setae increases with increasing surface energy. Based on this, Hiller (1968, 1969, 2000) concluded that attachment in geckos occurs by way of intermolecular forces, although the type of forces that dominate could not be conclusively determined.

Based upon measurement of attachment forces generated by individual setae, intermolecular attachment was confirmed (Autumn et al. 2000, 2002; Autumn and Peattie 2002). A single seta of *Gekko gecko* was shown to be able to produce up to 200 μN of force, consistent with estimated values of setal force of 40–400μN obtained from a mathematical model based on the Johnson–Kendall–Roberts theory of van der Waals forces (Johnson et al. 1971; Israelachvili 1992). These investigations implicated intermolecular forces but were not able to clearly distinguish between the roles of capillary adhesion and van der Waals forces (Autumn et al. 2000; Autumn and Peattie 2002). Subsequent experiments were directed toward ascertaining the type of force primarily responsible for adhesion in gekkotans.

van der Waals interactions are primarily dependent on the amount of contact area and the separation distance between the contacting surfaces, and thus require extremely close contact for the generation of substantial adhesive forces (Rimai and Quesnel 2001). The strength of these forces also depends directly upon the polarizability of the surfaces and is not directly related to surface polarity (Rimai and Quesnel 2001). Since van der Waals forces are universal and do not require the presence of a permanent dipole, an adhesive system configured to exploit them would be capable of adhering to almost any polarizable surface. In contrast,

Fig. 1 Continued

region of each scansor, and these overlie the setae of the next most proximal scansor. C. SEM of a series of lamellae that clothe the ventral surface of the digit proximal to the toe pad proper. The lamellae lack the reticular vascular networks and connections to the lateral digital tendons (see Fig. 2B) that are typical of scansors. D. Schematic diagram of the operation of the scansors during application and release of the setae. In panel D(i) the toe pad is unfurled from its hyperextended state (see Fig. 2A), driving the canted setae (depicted in gray) toward the substratum (depicted here in smooth and rough conformations). As the setae become adpressed to the substratum their angle relative to the substratum lessens. Those setal tips that come into sufficiently close contact with the substratum make van der Waals adhesive contact while others remain unattached. Tensile loading on the attached setae is imparted through the stratum compactum of the dermis (black posteriorly-directed arrow) which is continuous with the lateral digital tendon (ldt), bringing about the forces measured in frictional adhesion. Panel D(ii) depicts the release mechanism. Relaxation of tension on the ldt (black anteriorly-directed arrow) relieves the tensile loading. The toe pad is then hyperextended, raising the setae to the critical detachment angle (30° for *G. gecko*; Autumn et al. 2000), resulting in the breaking of the van der Waals adhesive bonds and release of the setae. The staggered length of the setae results in all setae on a scansor attaining the critical release angle simultaneously.
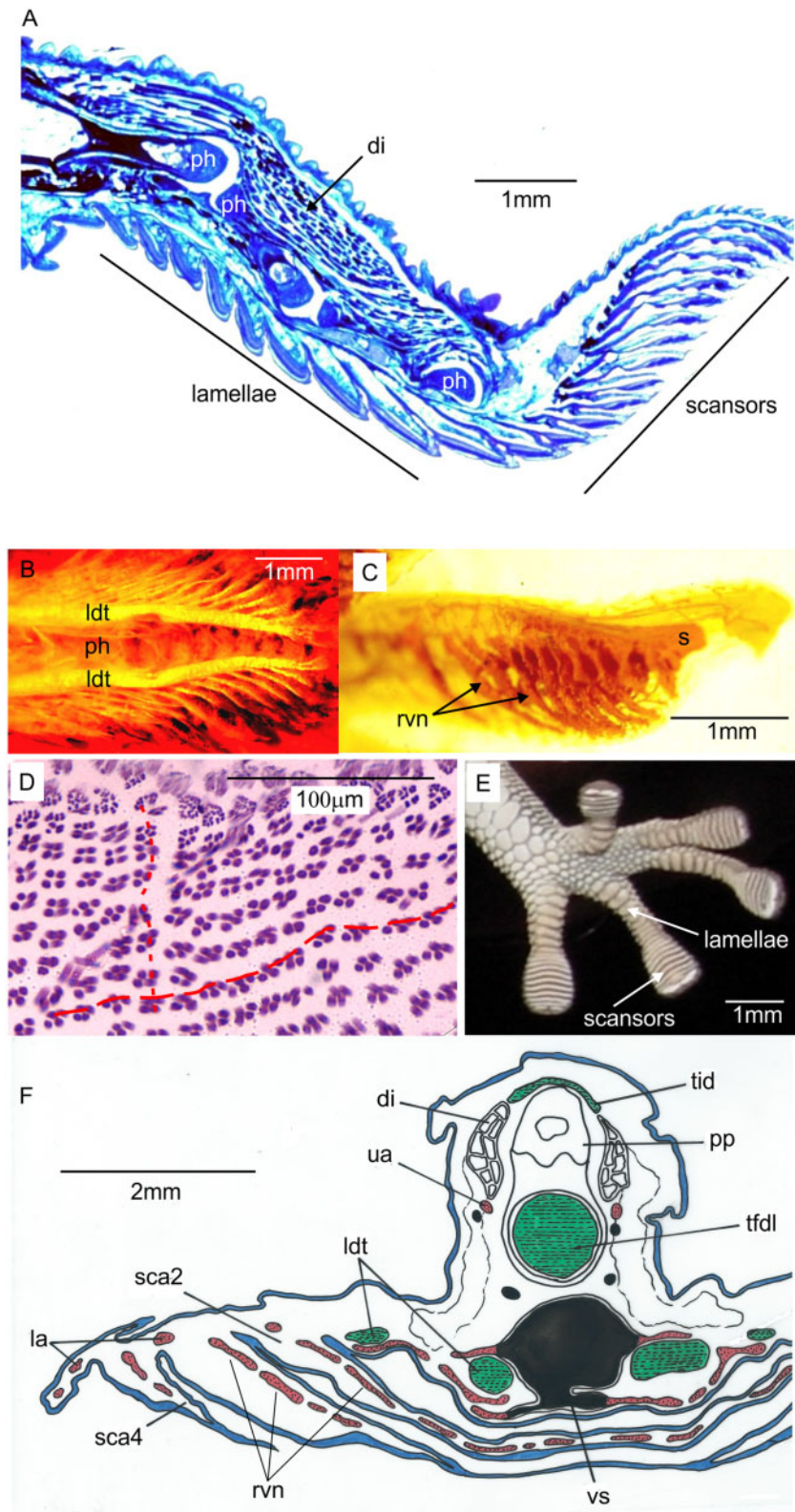
Fig. 2 Structural components of the toe pads and digits of geckos. **A**. Parasagittal section through digit IV, left pes of *Thecadactylus rapicauda* in the hyperextended state. The scansors reside on the hyperextensible region of the digit whereas lamellae clothe the more proximal region of the digit. The dorsal interossei muscles (di) situated dorsally in the digit power digital hyperextension, this action being facilitated by modifications of phalangeal (ph) anatomy. **B**. Dissection of the lateral digital tendons (ldt) of digit IV, left pes of *G. gecko* showing their branches to each scansor, which become continuous with the stratum compactum of their dermis. The channel between the ldts was occupied by the now-removed phalanges (ph). **C**. Microfil injection of the central vascular sinus (s) and reticular

capillary forces result from the surface tension of a layer of liquid between two contacting surfaces (Petrucci and Harwood 1993), which can act as an adhesive if surface wettability is high (i.e., contact angles are low) (Huber et al. 2005; Sun et al. 2005; Kim and Bhushan 2008). The water tension formed between two surfaces is resistant to perpendicular forces, but will slide along the surface, and thus functions best on rough surfaces, with asperities that can act as anchor points for the fluid. Unlike van der Waals forces, capillary forces do not depend upon contact area, and are not related to the size of the contacting structures.

The inability of geckos to stick to hydrophobic, weakly polarizable surfaces (i.e., polytetrafluoroethylene, commonly known as Teflon^{TM}) could have been due to either reduced capillary adhesion or reduced van der Waals forces (Autumn et al. 2002). To resolve this problem, polarizability was separated from hydrophilicity/hydrophobicity, revealing that single setae are able to attach equally well to both hydrophilic and hydrophobic polarizable surfaces, suggesting that van der Waals forces, rather than capillary forces, are the primary mechanism of attachment in gekkotans (Autumn et al. 2002). Additional support for attachment via van der Waals forces resulted from the discovery that setal mats (Fig. 1A, B) are superhydrophobic (Autumn and Hansen 2006; Liu et al. 2012), which likely reduces the effectiveness of capillary adhesion (Autumn et al. 2002).

Even so capillary, or capillary-like, forces may play a significant role in attachment (Huber et al. 2005; Sun et al. 2005; Pesika et al. 2009), although adhesion is possible without their contribution (Autumn and Peattie 2002). Spatular pull-off forces increase with increasing relative humidity, indicating that a water layer between spatulae and the substrate may play a role in enhancing adhesion (Huber et al. 2005; Sun et al. 2005), although a large drop in adhesive strength occurs when the adhesive system is submerged in water and attached to a hydrophilic substrate (Stark et al. 2013). Huber et al.(2005) suggested that water layers may contribute to adhesion in a different way, and theorized that adsorption of water molecules by the setal spatulae could change their effective short-range interactions, enhancing van der Waals adhesion. Puthoff et al. (2010), Prowse et al. (2011), and Chen and Gao (2010), however, intimated that the increase in adhesion as humidity increases is related to material changes, rather than capillary adhesion (i.e., setae get softer in high humidity, thereby making more contact). Contact electrification has also been advanced as the source of adhesive forces (Izadi et al. 2014), it being argued that electrostatic interactions, rather than van der Waals or capillary forces, dictate the strength of gecko adhesion. This explanation has yet to be incorporated into biomimetic simulation attempts.

In their initial observations of adhesive attachment of gecko setae, Autumn et al. (2000) noted that the direction of application of the setal tips, the angle of the setal shaft (Fig. 1A), and the tensile loading (Fig. 1D) applied to the setal shaft were all contributory to the magnitude of attachment forces recorded. The recognition that tensile loading applied parallel to the surface resulted in a major increase in setal attachment force led to a renewed examination of frictional forces (Autumn et al. 2006a; Tian et al. 2006). Conventionally, friction is described as a contact interaction between two surfaces that opposes their relative motion, thus preventing slippage (Resnik et al. 1992). Friction at a macroscopic scale is proportional to, and depends upon, the normal force, which acts perpendicular to the surfaces, pushing them together (Cutnell and Johnson 1995). It also depends upon the coefficient of friction of the two surfaces, a parameter that relates to their surface properties. A frictional force may be static (acting on a stationary object) or kinetic (acting on a moving object), and the coefficient

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Fig. 2 Continued
vascular networks (rvn) of the toe pad of digit IV, left pes of *G. gecko*. **D**. Frontal section (stained with hematoxylin and eosin) of some of the setae of a scansor of digit IV, left pes of *G. gecko* showing the setal stalks arranged in tetrads and indicating their arrangement in rows across the width of the scansor (red, long-dashed line) and ranks proximodistally along the length of the scansor (red short-dashed line). **E**. Ventral view of the left pes of *Rhoptropus biporosus*, a species in which the demarcation between the toe pad and its scansors and the lamellae of the more proximal region of each digit is abrupt. **F**. Diagrammatic rendition of a cross-section of the distal region of digit IV, left pes of *G. gecko* indicating the structural components of the toe pad. di, dorsal interossei muscles; la, lateral artery; ldt, branches of the lateral digital tendon system; pp, penultimate phalanx; rvn, branches of the reticular vascular networks of the scansors; sca 2 and sca 4, portions of scansors 2 and 4 of the four scansors captured in the plane of the section (see panel A for an appreciation of the overlap of scansors when seen in cross-section); tfdl, tendon of the flexor digitorum longus muscle; tid, tendon of the dorsal interossei muscle; ua, ungual artery; vs, venous sinus.

of friction varies in relation to this. Friction acts parallel to the surface and is independent of both contact area and speed (Cutnell and Johnson 1995). On inclined surfaces frictional forces may help an animal maintain traction, but the animal will slip if the component of its weight parallel to the surface exceeds the force of static friction. Furthermore, on perfectly vertical surfaces the force of static friction is zero because the gravitational force has no component perpendicular to the surface (Cartmill 1985). Similarly, as frictional forces act only in shear (Bhushan 1992) they cannot aid in adhesion beyond the vertical (on overhangs). It is these characteristics of frictional forces that initially led their rejection as the primary mechanism of adhesion in geckos.

The operation of frictional forces at a microscopic scale, however, differs. Amonton's laws (Bowden and Tabor 1966) state that friction is independent of the surface area of an object. Although this is so for macroscopic surface area, it does not hold at the molecular level, for which the strength of a frictional force is proportional to the true area of contact between two surfaces (Bowden and Tabor 1966). At the molecular level surfaces are not smooth but instead bear many asperities and the true contact between the surfaces is limited to discrete contact points (Fig. 1D), with only a fraction of the area being available for contact than would be the case if the surfaces were perfectly smooth (Bowden and Tabor 1966; Bhushan et al. 1995). Adhesion via van der Waals forces depends largely upon the closeness of contact between two surfaces (Fig. 1D), as these forces dominate at very small separation distances (<10 nm) (Rimai and Quesnel 2001). The highly branched nature of setae and their very numerous, very small spatular tips provide increased contact area (Niewiarowski et al. 2016) and enhance van der Waals adhesion as well as friction between them and the substratum, thereby increasing the "adhesion component" of friction and enhancing the frictional interaction between the animal and the surface. This suggests that complex, branched setae that contact the surface more efficiently may act better as frictional surfaces than would less complex structures. The clear link between frictional and adhesive forces (Autumn et al. 2006a; Tian et al. 2006) resulted in the proposal of a new model, "frictional adhesion," to explain the attachment of gecko setae (Autumn et al. 2006a). The force produced by gekkotan setal fields has both frictional (shear) and adhesive (intermolecular attraction) components (Fig. 1D), and shear forces are generated via anatomical modifications within the feet

(Fig. 2) and through the use of opposing foot placement on inverted surfaces, allowing adhesion even in this situation (Autumn et al. 2006a).

In general, a shear force of at least double the adhesive force is required for the adhesive force to be maintained (Autumn et al. 2006a), and measurements from isolated setae of 200 μN of shear force and 40 μN of adhesive force (Autumn et al. 2000, 2002) suggest that this factor may often be exceeded. The frictional adhesion model helps to explain how detachment of setae occurs. The relationship between the two forces is consistent with a critical detachment angle (Fig. 1D) (that for Tokay geckos [Gekko gecko] being approximately 30°—Autumn et al. 2000). At shear forces less than twice the adhesive force, and at an angle of greater than the critical detachment angle, adhesive forces can no longer be maintained and setae will release from the surface with no measurable detachment forces (Autumn et al. 2006a).

Setae are inherently self-cleaning structures, and represent the first self-cleaning adhesive discovered (Autumn 2006a; Autumn et al. 2014). After contacting a dirty substrate, geckos can actively and passively self-clean their adhesive system through continued use, unlike other pressure sensitive adhesives (PSAs) which become useless when fouled (Hansen and Autumn 2005; Hu et al. 2012). They are also unidirectional structures with a non-sticky default state, preventing inappropriate adhesion to surfaces (Autumn and Hansen 2006). To achieve attachment, individual setae require both a perpendicular and a parallel preload (Fig. 1D) to maximize attachment forces (Autumn et al. 2000), with the loading occurring in the direction of setal curvature (Fig. 1A). Maximally attached setae are loaded in tension (Peterson et al. 1982; Peattie 2009) and held at a low angle (less than the critical detachment angle) relative to the substrate (Fig. 1D).

Multiplication of β-keratin genes has been positively correlated with the developmental expression of setae (Liu et al. 2015). The β-keratin of which setae are composed is a very stiff material with a fairly high elastic modulus (Autumn et al. 2006b). Fine subdivision of setal tips and the high aspect ratio of the setal shafts (Fig. 1A) result, however, in a considerable decrease in the effective elastic modulus of the β-keratin, allowing setae to act as flexible attachment structures and to conform more easily to irregular surfaces (Autumn et al. 2006b, 2014). The setal fields on the scansors (Fig. 1B) act as a tacky, deformable material, with the effective elastic modulus of the fiber array in deflection at

the setal bases being four orders of magnitude less than that of the setae when loaded in tension (Autumn 2006a). Setae have dimensions (Russell et al. 2007) that are conducive to their behavior as PSA structures, enhancing their ability to conform and adhere to microscopically rough surfaces and to comply with surface irregularities (Fig. 1D) (Jagota and Bennison 2002; Campolo et al. 2003; Persson 2003, Persson and Gorb 2003; Persson et al. 2005; Spolenak et al. 2005; Autumn et al. 2006b). Such properties exploit both the high tensile strength of β-keratin (Bonser and Purslow 1995; Bonser 2000), resulting from its proteins being polymerized into long cables (Dalla Valle et al. 2007), and the lesser elastic modulus resulting from its elaboration into cantilevered beams (Fig. 1A) (Zhao et al. 2009; Hu and Greaney 2014) that enhance adhesion via van der Waals interactions.

Assessing how adhesion originated

The transition from spinules to adhesive setae has recently been explored in the genus *Gonatodes* (Russell et al. 2015; Higham et al. 2017), a group of dwarf geckos found across South and Central America. One species within the genus, *G. humeralis sensu lato*, is frequently found sleeping on smooth leaves, and exhibits a geographic distribution that is much larger than that of its congeners (Pinto et al. 2019). In biomechanical tests, *G. humeralis sensu lato*, but not other species in the genus, is capable of ascending a smooth vertical surface (Higham et al. 2017), providing evidence that it possesses a rudimentary adhesive system. At the inflection points on the digits this species exhibits relatively long epidermal outgrowths (10–15 μm) compared with other species, and the longest of these are true setae (Russell et al. 2015). They are branched distally and have spatulate tips. This appears to be the modification that would be considered to be part of an adhesive system, suggesting that enhanced frictional capabilities likely preceded the development of a true hierarchical adhesive apparatus with fully developed toepads and associated internal structures typical of the system (Fig. 2). Such species with incipient adhesion provide a window into the evolutionary paths, and ecological conditions, associated with the origin of adhesion and the accumulation of small changes that sum to bring about a macroevolutionary transition (Bock and von Wahlert 1965; Higham et al. 2017; Russell and Gamble 2019; Higham et al. 2019).

Documenting the structure of setal fields and their underlying anatomical associations

Exploration of the mechanism of gekkotan setal adhesion has been accompanied by studies attempting to understand the structure and function of the entire adhesive apparatus (Hora 1923; Dellit 1934, 1949; Mahendra 1941; Ernst and Ruibal 1966; Maderson 1970; Russell 1975, 1976, 1981, 1986, 2002; Russell and Bauer 1990a, 1990b; Russell et al. 1997). Although gekkotan setae (Fig. 1A) have been described on numerous occasions (Ruibal and Ernst 1965; Schleich and Kästle 1986; Autumn 2006b; Dalla Valle et al. 2007), variation in their form is poorly understood, both within and between species (Autumn 2006a). Investigations of setal form and variation in the Tokay gecko (*G. gecko*) (Russell et al. 2007), and the southern African *Rhoptropus* radiation (Russell and Johnson 2007, 2014; Russell et al. 2007; Johnson and Russell 2009) reveal that setal length varies considerably from the distal-most to the proximal-most scansor (Fig. 1A, B), and that basal diameter, tip dimensions, tip area, tip density, and total spatulate tip area are distributed differently across the subdigital pad. Thus, there is no typical seta (Fig. 1A–C), and each scansor has a particular pattern that differs from that of its adjacent neighbors. Although individual characteristics, such as the average area of each setal tip, and average tip density per unit area, change along the length of the pad, total setal tip area (which relates to the total adhesive force potentially able to be generated) varies much less, indicating the potential for compensatory changes within the toe pad that are of importance for functional interactions relating to the creation and release (Fig. 1D) of the adhesive interactions in different regions of the digit. Such variation within the confines of even a single digit indicate that variation across the pad likely relates to differences in the mechanics of interaction with the substratum in different regions of the digits of geckos.

Consideration of the appropriate configuration of gecko-inspired adhesives has provided context for understanding of the form of gekkotan setal fields. Schargott (2007) suggested, based upon general design principles related to fibrillar arrays, that stiffness of the array can be reduced by tilting the beams, resulting in a structured surface with tilted elements. Such ideas help in the interpretation of observed patterns of setal fields in geckos (Fig. 1A, B). Gekkonid setae are held in a tilted configuration (Fig. 1A), affecting their directionality as adhesive structures (Fig. 1D) (Autumn 2006a), and show

variation in length along the subdigital pad (Fig. 1) that may be related to an avoidance of matting when the setae are deployed (Schargott 2007).

The totality of the adhesive system is complex and many components of foot structure, including integumentary, muscular, skeletal, tendon, and vascular contributions (Fig. 2), work together to control the actions of the setae (Tian et al. 2013) in relation to adhesion and detachment during locomotion (Russell 1975, 1981, 2002). Although the gecko adhesive system is broadly regarded as a key innovation (Niewiarowski et al. 2016, 2017), this hypothesis has failed to be supported in at least two studies (Gamble et al. 2012; Garcia-Porta and Ord 2013).

The digits of some pad-bearing gekkotans undergo distal to proximal hyperextension during locomotion (Russell 1975), whereby the digits are rolled off the surface and then rolled back onto it from proximal to distal to effect attachment (Figs. 1D and 2A) (Russell 1975). These movements are controlled by the muscles of the digits (Fig. 2A) (Russell 1975), and are likely monitored by cutaneous sensilla in localized patches on the dorsal surface of the digit (Lauff et al. 1993; Röll 1995). The process of hyperextension (Fig. 2A) (whether distal to proximal or vice versa; Russell and Bels 2001; Higham et al. 2017) likely plays a major role in the deployment and detachment of setae (Fig. 1D), and therefore locomotion (Russell and Higham 2009). During detachment, hyperextension may act to deflect setae past the critical detachment angle, resulting in their release from the surface (Autumn et al. 2000; Russell 2002). Furthermore, during attachment, unrolling the digits onto the surface pushes the setae forward, producing a larger area of contact with the substrate and aligning the setae appropriately with the surface prior to the application of tension that results in sliding (Fig. 1D), causing the spatulae to become well-aligned and ordered (Zhou et al. 2013), thereby enhancing adhesion (Russell 1975).

The lateral digital tendons (Fig. 2B) send at least one branch to insert on each scansor of the subdigital pad (Russell 1976), promoting adjustment of the tension imposed on individual scansors (Russell 1975, 1976), and application of the parallel preload required for generating shear force that is transmitted to the individual setae (Fig. 1D) (Autumn et al. 2000; Russell 2002). The vascular system of the digits (Fig. 2C, F) seemingly plays a role in adhesion and in the deployment of setae (Russell 1981, 2002), with the sinuses and their associated reticular networks (Figs. 1B and 2C, F) allowing the subdigital pad to conform to surface irregularities (Russell 1981). Increased pressure in the subdigital sinuses may

also contribute to the perpendicular preload required to engage setae with the substrate (Autumn et al. 2000; Russell 2002).

Gekkotans possess the unique ability to adhere to surfaces in any orientation, even completely inverted. Thus, their anatomical components must be able to operate such that contact can be effective in a variety of body configurations and patterns of whole body loading (Russell and Oetelaar 2016). In overhanging and inverted orientations geckos cannot employ gravitational forces to aid in the generation of either the parallel or perpendicular preloads required for setal attachment, and must therefore be capable of generating them internally, possibly through the combination of the actions of the lateral digital tendon system (Figs. 1D and 2B), which is controlled through the metapodial–phalangeal joint capsules and plantar aponeurosis complex (Russell 1993) by the gastrocnemius complex of muscles, and subdigital blood sinuses (Fig. 2C, F) (Russell 2002), as well as through highly controlled foot placement (Russell 1975; Autumn et al. 2006a).

Performance aspects—real world functional demands and gecko adhesion

Geckos are able to hold station on vertical surfaces, implying that frictional loading can be maintained passively (Hiller 1968; Bergmann and Irschick 2005; Stewart and Higham 2014) for long periods while the animal remains static (Russell and Oetelaar 2016). To be effective on overhanging surfaces, this loading must be applied actively in parallel to the locomotor substratum, opposing, rather than with the assistance of, gravitational loading (Peattie 2009). The intimate contact between integument, dermis, subdermal lateral digital tendons, and joint capsules and limb muscles (Figs. 1D and 2A, B, F) is implicated in this chain of control (Russell 1981). Evidence gained from calculations based upon isolated setae indicate the theoretical potential of the functional system, but observation of input forces, and the timing of these, in the intact animal are needed to indicate how geckos control adhesion in the rapid-fire force modulation required for fast locomotion (Russell 1975; Autumn et al. 2006c), and in the long-term loading important in station holding.

The specific dimensions of setae and their arrangement into setal fields (Fig. 1A, B) may provide certain functional benefits for enhancing and maximizing adhesive effectiveness. The adhesive system of gekkotans has often been modeled as a mat of fibrillar microstructures that is brought into contact with

a surface (Jagota and Bennison 2002; Glassmaker et al. 2004; Hui et al. 2004). The reliance of the system on van der Waals forces for initiating adhesion (Fig. 1D) with the surface (Autumn and Peattie 2002; Autumn et al. 2002), before larger shear forces can be induced (Fig. 1D) (Autumn et al. 2006a; Tian et al. 2006), is predicated upon extremely close contact between the setae and the locomotor surface. The performance of such a system depends primarily on the mechanical control of the contacting structures as well as their geometry and material properties (Hui et al. 2004; Spolenak et al. 2005). The primary advantage of a fibrillar structure is that it allows for increased compliance between the fibers and the surface (Fig. 1D), leading to increased contact and adhesion on rough surfaces with a variety of wavelengths and asperity heights (Fig. 1D) (Jagota and Bennison 2002; Glassmaker et al. 2004; Hui et al. 2004; Spolenak et al. 2005). This interpretation can be extrapolated for relatively uniform substrata, but is also locally applicable for highly irregular and/or highly undulant surfaces that are contacted by complete setal fields (Russell and Johnson 2007).

On any given footfall on undulant locomotor surfaces the presence of multiple spatulate tips on the setae possibly provides compensation in local patches because only small portions of the adhesive system will encounter regions of the substratum with which they can make effective contact. For geckos, setal fields (Fig. 1A, B) and their component scansorial subunits (Figs. 1B and 2 A) are large and deep in comparison to the physical attributes of the terrain traversed (Russell and Johnson 2007), and will bridge across high points rather than conforming to the contours of the undulant surface (Fig. 1D). Whereas smooth surfaces provide expansive areas for potential contact, rougher and more undulant surfaces provide only local patches with which intimate setal contact can be made (Fig. 1D). In real world situations gecko adhesion is operationalized in circumstances that provide only limited opportunities for making such contact. This likely accounts for the enormous adhesive capacity of the system as a whole (Russell and Johnson 2007; Higham et al. 2019).

The irregularity and randomness of asperities of the scale and distribution evident in the rock surfaces on which species of *Rhoptropus* live (Russell and Johnson 2007), and the unyielding nature of the locomotor substratum, all indicate that fields of setae may provide a locomotor advantage that individual setae alone might not suggest. Fields of setae (Fig. 1A, B), given the random distribution of available support areas (Fig. 1D), allow islands of suitable substratum to be located and utilized in any body orientation. Setal fields may be particularly suited to undulant and unpredictable surfaces (Russell and Johnson 2007) where contact is likely to be patchy and limited. Indeed, the effectiveness of adhesion is predictable by the ratio of scansor (Fig. 2A, E) dimensions to surface feature dimensions (Gillies et al. 2014). The complex configuration of setal fields implies that a simple mat of identical setal structures may not be sufficient to provide adequate attachment to the surfaces these animals move on, and that the microvariation of setae along both scansors and digits (Fig. 1A–C) allows for optimal contact and adhesion on natural substrates. This region-to-region variation in setal field configuration likely has implications for ongoing attempts to fabricate synthetic seta-like adhesives that strive to mimic the adhesive capabilities of geckos.

Interspecific scaling of the adhesive apparatus will have a significant impact on how geckos experience the real world, and could impact broad-scale factors like habitat selection. Multiple studies have examined the scaling of pad area to body mass (Bauer and Good 1986; Irschick et al. 1996), but different conclusions have been drawn. Under isometry, pad area should scale to mass$^{0.66}$, but under functional similarity the scaling exponent would be 1. Among species of *Gekko*, pad area scales with body mass$^{0.59}$, and it was suggested that this negative allometry may be related to "overdesign" in small geckos (Bauer and Good 1986). Irschick et al. (1996) examined a wider array of pad-bearing lizard species, and uncovered a scaling exponent of 0.75–0.78, which represents positive allometry. However, this lack of functional similarity suggests a relative decrease in adhesive capacity as body size increases. Higham et al. (2017) examined the scaling of frictional adhesive force with body mass among anoles and geckos, and revealed a scaling exponent of 1.08 (0.95 when phylogenetic relationships were incorporated). Pad area was not measured given that geckos without toepads (but with adhesive ability) were included. This disconnect between the functional ability of the animal and the morphology (pad area) of the adhesive apparatus implies that other factors may be driving adhesive performance. As highlighted above, many features of the adhesive system may vary within and among species, including the length, diameter, compliance, and density of the setal fields (Fig. 1A, B) (Peattie and Full 2007). Additionally, the scaling of adhesive performance is likely substrate-dependent, adding an additional layer of complexity.

Bio-inspired design—the application of design principles from the gekkotan adhesive apparatus

The impressive adhesive capacity of geckos has led to hundreds of attempts to fabricate nano-scale adhesive devices that mimic the structure of gecko setae (e.g., Full 2001; Campolo et al. 2003; Geim et al. 2003; Glassmaker et al. 2004; Yurdumakan et al. 2005; Kim et al. 2007; Lee et al. 2008). Researchers have envisioned a wide variety of uses for gecko-like adhesives, including surgical aids (Mahdavi et al. 2008), climbing robots (Santos et al. 2008), manipulation of space debris (Jiang et al. 2017), and even football gloves (Autumn 2006a, 2006b). Evidence suggests that setae may act in a manner similar to PSAs (Autumn et al. 2006b), yet differ from conventional PSAs in that they do not adhere spontaneously (Autumn and Hansen 2006), are releasable, and are not subject to self-adhesion and degradation (Autumn 2006b). The majority of microfabricated structures to date have taken the form of fibrillar mats of cylindrical structures composed of various polymer materials (Autumn et al. 2002; Geim et al. 2003; Sitti and Fearing 2003; Peressadko and Gorb 2004; Northen and Turner 2005). Initially such simulacra required very high preloads (Geim et al 2003, Northen and Turner 2005; Yurdumakan et al. 2005) to induce functional adhesion, and generated forces well below the adhesive capacity of gecko setal fields. A few attempts have been made to model the hierarchical, branched structure of setae (Northen and Turner 2005; Kustandi et al. 2007), but these structures have not been capable of achieving "gecko-like" forces, possibly due to the perpendicular application to the substrate resulting in their buckling (Autumn 2006b; Kustandi et al. 2007), or the lateral adhesion of adjacent tips, both of which are common problems with fabricated microfiber arrays (Geim et al. 2003; Glassmaker et al. 2004).

Synthetic structures have been successfully produced at the nano-scale (spatular level), using silicone rubber and polyester materials fabricated with dimensions similar to those of setal tips, capable of generating adhesive forces of around 100 nN each, similar to expected values for real spatular tips (Sitti and Fearing 2003). More recently, synthetic structures with many characteristics of real setae have been successfully produced (Lee et al. 2008; Zhao et al. 2009; Sameoto and Menon 2010; Gorumlu and Aksak 2017). The stiff polymer fiber array produced by Lee et al.(2008) is capable of generating seta-level forces, with 1 cm^2 of the material being able to support up to 400 g. Furthermore, the adhesive was not applied to the surface perpendicularly, but pulled along it, which resulted in the generation of high shear forces. It is also re-usable and was the first micro-fabricated adhesive to mimic the non-sticky default state of gecko setae (Lee et al. 2008). Functionally-graded fiber arrays have been produced that adhere well to smooth and rough testing surfaces (Gorumlu and Aksak 2017). Fabricated polypropylene and high density polyethylene fibrillar surfaces subjected to load–drag–pull step cycles do not, however, have the same wear-free properties as gecko setae (Gillies and Fearing 2011). Tip shape also has a major effect on adhesive capabilities of synthetic microfilaments (Murphy et al. 2007); the mushroom-shaped tip is now widely considered to be the most successful, and is currently the most common morphology for gecko-inspired synthetics. Fabrication of simulated gecko setae has proved to be costly (Sameoto and Menon 2010), leading to the search for less expensive materials, such as cast polymers or carbon nanotubes with nanoscale spatulate tips (Ge et al. 2007), but these currently are plagued by issues relating to scalability and mass production (Sameoto and Menon 2009).

Several attempts to produce wall-climbing robots using gecko-like structures have proved successful. One such is "Mecho Gecko" (Full 2001), which climbs using a PSA and revolving structures that mimic the rolling of gecko digits onto and off the surface by hyperextension. Another robot, Stickybot, possesses hierarchical levels of compliance, from the limbs themselves down to microcompliant seta-like stalks (Santos et al. 2008), and uses directional micro-adhesive stalks modeled on gecko setae to effectively climb smooth vertical surfaces at speeds up to 24 cm/s. The stalks are finely controlled by a series of cables which provide the perpendicular and parallel preloads required for adhesion. These robots do not possess the fine setal control and branched setae found in geckos, but their ability to rapidly scale smooth vertical surfaces, and to be deployed in microgravity situations (Jiang et al. 2017) is impressive.

Whereas Stickybot (Kim et al. 2007) possesses some degrees of compliance and control of its attachment devices, the control mechanisms of artificial setal arrays remain crude by gekkotan standards. In depth studies of gecko setal field configuration and control may, therefore, be informative regarding capabilities that may or may not be realizable by artificial constructs. Our ability to exploit gekkotan adhesion (Russell and Johnson 2009) will continue to depend upon insights gained from biology and engineering that reciprocally illuminate one another. Indeed, several synthetic gecko-inspired models have

been used to test hypotheses about the complex natural system, allowing for strict parameter control that sheds light on how particular aspects of the natural system contribute to overall performance (Stark et al. 2016).

Understanding the real-world capabilities of the adhesive adaptability of gekkotan setal fields (Russell and Johnson 2007) may also assist in visualizing solutions to the problems of not only fabricating gecko-inspired microfibrillar arrays, but also of considering how these might be deployed in robotic applications. Selection has guided the scaling and configuration of the entire adhesive pad complex of gekkotans. Mimicking the incredible moment-to-moment and patch-to-patch adjustability of such a system is likely an unattainable goal, but an understanding of these operational capabilities will certainly be instructive in guiding our efforts to comprehend and adapt the principles without necessarily trying to duplicate the intricate details. In this regard, attempts to employ such basic principles without the added complexity of fibrils have led to the development of synthesized inextensible fabrics with thin elastomeric adhesive layers (Bartlett et al. 2012).

Grand challenges in gecko adhesion research

Our understanding of the principles by which gecko adhesion operates has advanced rapidly over the past 20 years and, rather than remaining in the almost exclusive domain of biologists that was typical of the research efforts prior to the turn of the millennium, has become a research focus of scientists working in quite disparate disciplines. To some extent collaborations have flourished and have led to exciting new insights, but of late breakthroughs have become less frequent because the remaining problems are increasingly challenging. Continuing to improve our understanding, and to more effectively employ the principles of gecko adhesion for human applications, will require greater intensity and scope of interdisciplinary research. We posit that this is an ideal time to facilitate the interaction between diverse fields and carve out a path for the future. Below we identify several grand challenges that present opportunities for the building of teams and for the application of knowledge from different disciplines to seek solutions. Delving more deeply into the characteristics of gecko adhesion, a nanoadaptation that has been honed in nature for at least 100 million years, will be vital to the employment of the underlying principles for human applications.

(1) Employ the diversity of geckos to understand how the adhesive system is tuned to environmental challenges. The enormous diversity of geckos (there are over 1800 species) (Bauer 2019) provides a rich background for exploring how different taxa have "solved" various environmental challenges related to the functioning of their adhesive system, which has evolved on multiple occasions from non-adhesively competent precursors (Russell and Gamble 2019). Geckos are circumglobal in their distribution and latitudinally widespread, and thus occupy habitats that vary in such aspects as roughness, wettability, polarizability, cleanliness, and compliance (Higham et al. 2019; Stark and Mitchell 2019). Understanding evolutionary pathways and biomechanical configurations that have led to adaptation to various and varying conditions can assist us in determining whether gecko-inspired adhesives should be custom-designed for different applications. Focus on the configuration of entire setal fields (Fig. 1A, B), rather than the configuration of a single seta, will likely assist biomimeticists in their quest to design and develop fibrillar arrays most suitable for particular applications.

(2) Explore developmental pathways that determine setal structure (both molecularly and physically) associated with taxonomic and setal field diversity. We know little about what programs the configuration of gecko setae and setal fields (Fig. 1A, B). Genomic exploration of what underlies the patterns of expression of fibrillar adhesives (Gamble 2019) will provide information about how and why they are constructed and configured the way they are, and whether there are differences related to particular environmental challenges. This will provide fertile ground for interactions between systematists, ecologists, genomic biologists, biomimeticists, and engineers for the development of task-effective synthetic setal arrays.

(3) Enhance our understanding of how geckos actually use their adhesive system in nature to improve our conceptualization of how gecko setae function. Investigation of how geckos partition their activities relative to different surfaces that they encounter, how they behave on different surfaces, and how their adhesive system is arrayed to accommodate these various challenges (Imburgia et al. 2019) can provide valuable insights into how their adhesive system operates. Beyond the basic ability to adhere,

geckos move freely on surfaces that exhibit a broad range of characteristics, so enhancement of our knowledge of how they cope with such varying conditions during rapid and acrobatic movement will be of importance to those wishing to adopt the principles of gecko adhesion for application to robotics and for determining design principles for other biomimetic applications. It is evident that many geckos with an adhesive system also exhibit claws as alternative tractive devices. We know little about the circumstances under which these different means of surface contact are used, and whether or not they are used alternately or in combination. What environmental circumstances favor this double indemnity approach (Naylor and Higham 2019), and what circumstances favor the reduction or loss of claws or the reduction or loss of the adhesive apparatus? Insights from such understandings can be instructive for biomimeticists and engineers working in collaboration with ecologists and biomechanists in their quest to determine under what conditions fibrillar adhesion is favored.

(4) Improve our understanding of how gecko-inspired synthetic adhesives perform under combinations of variable environmental conditions. The real-world conditions in which gecko-inspired synthetic adhesives will be used demand that more investigation of how synthetics perform outside of pristine laboratory conditions is needed. This includes the impact of wet and/or rough substrates (Niewiarowski et al. 2019; Stark and Mitchell 2019). The characterization of roughness is a major challenge to understanding the functioning of both gecko setae in nature and synthetic setae in biomimetic applications (Higham et al. 2019). In nature geckos are exposed to multiple fluctuating environmental conditions, but we understand relatively little about how their adhesive system might be tailored to them. For synthetic systems variation in substrate roughness and other environmental attributes are extremely likely to impose themselves during consumer use, making the development of a versatile, easy-to-use adhesive critical.

(5) Compare, contrast, and synthesize the diversity of fibrillar adhesives in the natural world. Fibrillar adhesives are expressed in a variety of animal groups and considerable progress has been made in understanding how these operate in various groups of arthropods. Reciprocal comparative observations and investigations of the higher order principles that govern the structure and function of animal-derived fibrillar adhesives (Drotlef et al. 2019) will provide a more complete picture of the fundamentals of such adhesives, and will be vital to our understanding of how they are affected by issues of size and scaling. Different groups of organisms are constrained in their evolutionary responses to environmental challenges by their history. Understanding such aspects of contingency will assist in determining what is necessary and sufficient for the operation of such systems, thereby helping us to ascertain what aspects are most important in the development of bioinspired synthetic adhesives.

Conclusion

The adhesive capabilities manifested by geckos result in the ability to reversibly attach to a wide array of surfaces in an astonishing array of body orientations and movement regimes. The interaction between the fields of microfibrillar arrays of the digits and the substratum, whether smooth, rough, or undulant, depends upon the structural properties of an integument of β-keratin that is locally modified to operate as a directional, pressure-sensitive adhesive. Adhesive attachment by geckos can be deployed and released rapidly as a result of a complex structural hierarchy of control mechanisms allowing moment to moment adjustment to topological and material changes in circumstance. In the living world, these capabilities are restricted to animals that are small by human standards. Attempts to microfabricate adhesives that mimic the properties of gekkotan setae present challenges that are rapidly being met. Employing such synthetic arrays at larger scales, however, may require a deeper understanding of how geckos adjust their available setal field surface area as they grow (Webster et al. 2009) and what the limitations are that seemingly restrict geckos to rather modest sizes. The basics of gekkotan adhesion are now quite well understood, but the dynamic employment of this phenomenon in very challenging nano-environmental circumstances promises to present the biomimetic community with significant challenges for the foreseeable future. We believe that interdisciplinary work is necessary to meet them.

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