CITRUS FRUITS INSPIRE THE NEXT GENERATION OF AIRBORNE DRUG DELIVERY

In this article, Andrew Dickerson, PhD, Assistant Professor, University of Central Florida – Mechanical & Aerospace Engineering FaST Lab, discusses recent research undertaken by his team into the mechanics of liquid microjets created naturally by citrus fruits, and how they could be the key to a new design of drug delivery device.

WHAT WILL CITRUS-INSPIRED TECHNOLOGY ENABLE?

Liquid microjets have been of interest to the scientific community for their use in dermal drug delivery,[2–3] micro-fabrication,[4] and chemical synthesis.[5] Microjet technologies have been made possible by careful control of piezo-electric drivers, microfabrication of precision nozzles and carefully tuned fluid properties. It is critical to control the breakup distance of these jets, so that the drops they produce find the intended location and are of the correct size. Traditionally, technologies which produce tuned microjets require precision-machined parts, pumps and electronic controls, which carry a large cost. While studies of synthetic microjet production and use abound, few have considered the microjets found in nature, which may provide alternative methods for robust jet production through the clever choice of materials and geometry, without the need for cumbersome supporting systems.

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In inhalable drug delivery, drug dispersal has been accomplished by atomising fluids by forcing them through a nozzle at high-speed, as is the case with a standard metered dose inhaler (MDI), or by allowing a liquid to transition into an easily inhaled vapour, such as with a nebuliser.

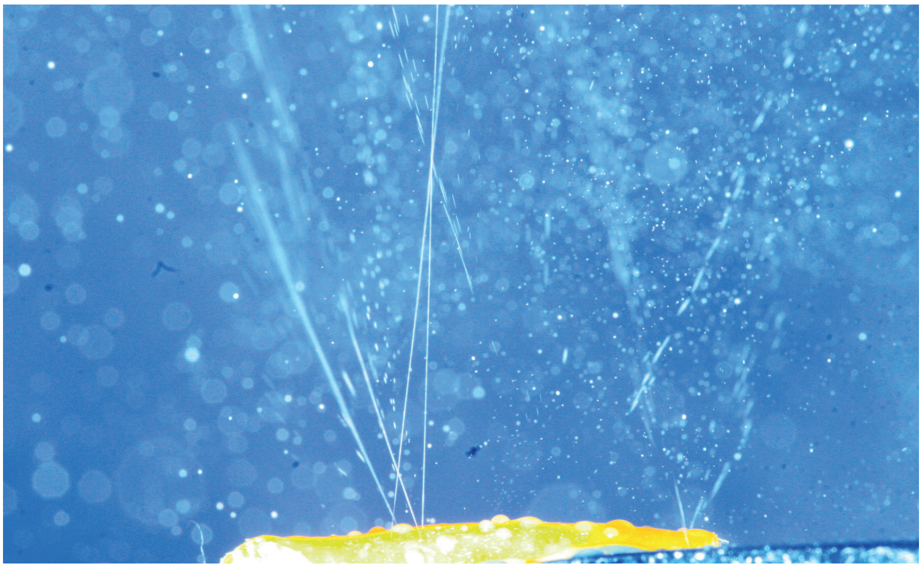

Figure 1: Image of oil jets issuing from sub-surface oil glands in the highly bent peel of a navel orange. The highly unstable jets issue at velocities that produce motion blur in the photo, giving the appearance of jet stability over longer distances.[1]

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The former technique allows inhaled doses to be portable and administered when required. Many patients need inhalers for emergency use and may never consume the many doses available in the device before expiration. The resulting added cost to the consumer and cost-prohibitive dispersion of such devices to underserved populations can be remedied with lower-cost manufacturing and single-use devices.

The microjets which emerge from citrus peels[1] under bending loads may provide the secrets for how to disperse fluid from disposable, single-use devices. Such devices can be easily tailored for dose quantity, rate and droplet size distribution. They will be easy to use, lightweight and appropriate for any fluid, from creams to the lightest and most volatile disinfectants. Applications may range from oral inhalation to dermal and ocular applications.

WHAT ARE CITRUS JETS?

The avid citrus consumer knows it is impossible to peel an orange and keep your fingers dry, even if the precious fruit inside remains unmolested. Others will have noticed the ephemeral and fragrant mist that is emitted when peels are broken and tiny fluid jets erupt into the air. The ejected fluid has a density about 80% that of water and a nearly identical viscosity. Even with the naked eye, one can appreciate the magnificence of these 100 µm diameter "citrus jets". With a macro lens and high-speed camera, the beauty of this inconspicuous event can become fully realised.[1] One such example is shown in Figure 1. These free jets are best witnessed after a fruit is carefully peeled and by bending the peel such that the zest, or rind, faces outward (Figure 1 & Figure 2a). Oil reservoirs reside in the albedo, a compressible foam-like layer commonly known as the "pith", which fills the space between the fruit locules and the thinner, stiffer flavedo or "zest".[2] The zest caps the reservoirs and shields the

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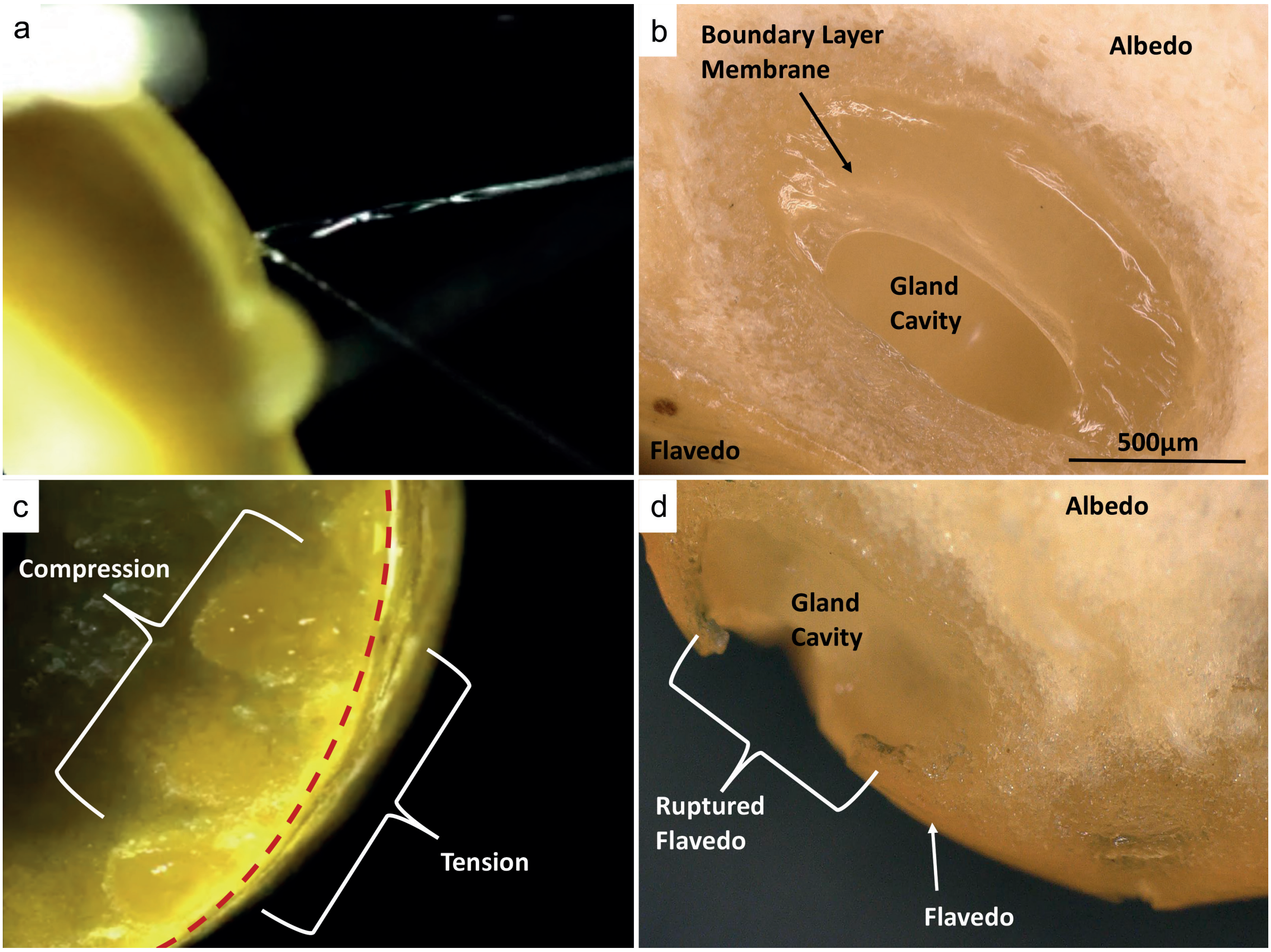

Figure 2: Microscopic images of (a) oil ejection from oil gland reservoir through the flavedo, (b) a cross- sectional view of a singular oil gland with boundary layer membrane partially intact, (c) a group of unbroken oil glands subjected to external bending, and (d) a cross-sectional view of an oil gland after rupture. The gland in (d) appears slightly collapsed due to ingress of the albedo toward the flavedo during rupture.[1]

fruit from the environment. Gland reservoir placement within the peel and relative size can be seen in Figures 2b and 2c. A layer of glossy boundary cells separates the oil in the reservoirs from the absorbent pith, which is clearly shown in Figure 2b, where the window into the reservoir is a fortuitous result of cutting.

It is believed all fruits in the citrus family have been developed by cross-breeding three core fruits in the last 1000 years: the mandarin orange, pumelo, and citron.[6] All citrus fruits tested in our study[1] exhibited oil jetting behaviour but, despite this shared characteristic, there remains no determinate evolutionary function of the oil, and no mention of oil atomisation in the literature to the author's knowledge.

Citrus jets are remarkably fast and very brief. We measured jet exit velocities across all hybrids within two weeks of purchase, finding a singular minimum of 1.58 m/s (mandarin) and singular maximum of 29.65 m/s (navel orange), with an average 8.47 ±4.03 m/s (n=545) across all species.[1]

The internal gauge pressure within the oil reservoirs enabling the average jet speed is about one atmosphere. A greater fluid pressure at the instant of zest failure produces faster jets.

MECHANICS OF MICROJET PRODUCTION

Bending the peel increases stresses in the zest, with the most perceptible increase in the direction normal to the dashed blue line drawn in Figure 3a-d, and increases pressure in the fluid.[1] The outer surface of a reservoir, as seen looking down onto a zest, can be seen in Figure 3b-d and is outlined by a dashed black ellipse. As the magnitude of bending increases, a failure precursor wrinkle forms on the zest surface atop the oil reservoir, as seen in Figures 3c and 3e. Further bending increases in-plane stress in the zest and fluid pressure below, inducing the brittle fracture seen in Figure 3d. The tear in the zest unveils a channel to the gland reservoir. The crack in Figure 3d begins atop the reservoir and is arrested by stomata surrounding the gland. Stomata are outlined in Figure 3e and are small, nearly circular voids in the zest.

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The strength of the zest topping each oil pocket governs how much fluid pressure can build. We also find the strength of the zest is related to its stiffness by applying theory from fracture mechanics.[1] The stiffer the zest, the faster the jets that rocket through it. This mechanism also requires the pith underneath the zest to be soft. In fact, it is two orders of magnitude softer. The zest is similar to acrylonitrile butadiene styrene (ABS) plastic, while the pith is like a foam pillow. Measurements of material stiffness were done with a tensile tester, which measures how much force is needed to stretch a material. Finite-element simulation (Figure 4) shows this contrast in material properties is key for jet creation, allowing the pith to compress while the zest is stretched. The greater the stiffness contrast between these two materials, the greater reservoir pressures bending the peel can accomplish. The final secret to a fast jet is the geometry of the oil reservoir, which is deeper than it is wide. This allows more of the fluid volume to reside in the region of the pith being compressed.

FLUID MICROJET STABILITY

Following emergence from a reservoir at nearly 10 m/s, jets rapidly break up into

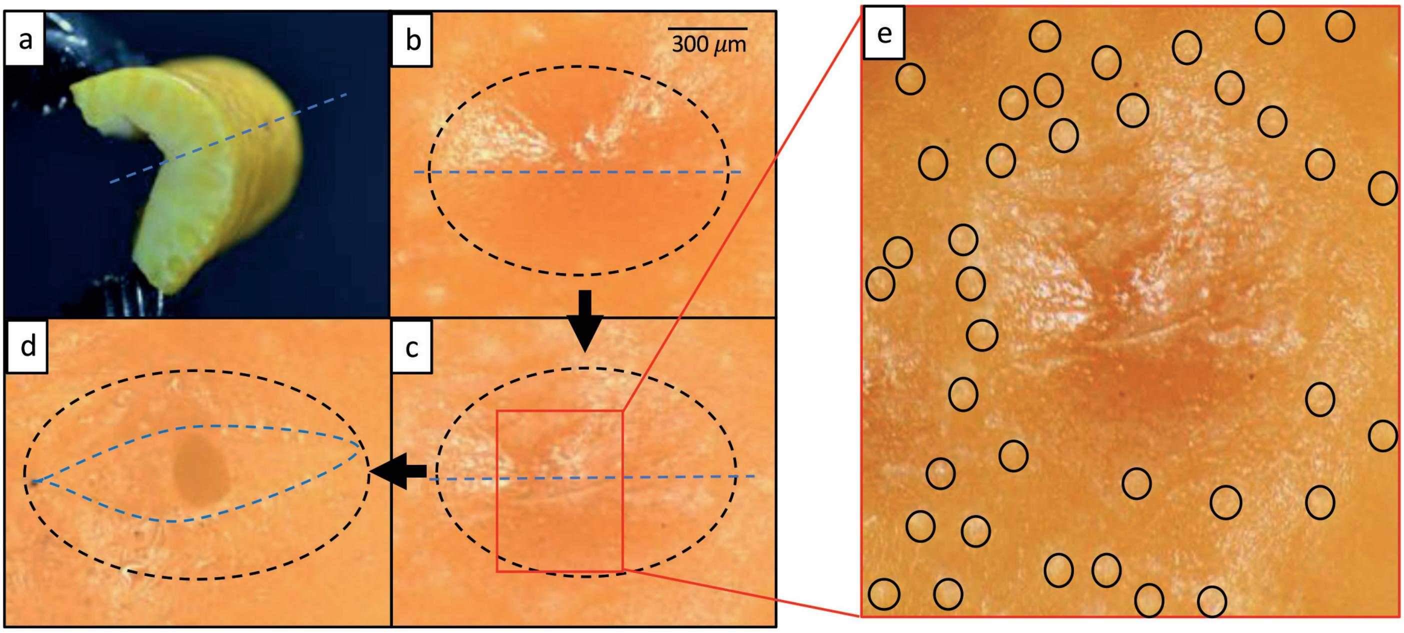
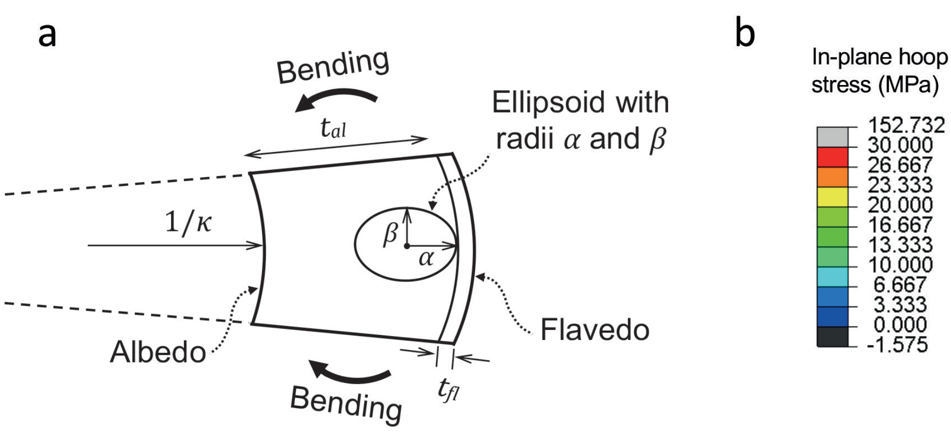


Figure 3: The process of glandular rupture. The process begins with bending a peel (a). From an external view of the flavedo, the unstressed gland in (b) is stressed to imminent failure in (c) and to failure in (d), which shows the channel leading to the oil reservoir. A zoom box of a crack forming prior to failure is shown in (e). Black dashes outline gland extents beneath the flavedo and the blue dashed lines represent the line normal to externally applied stress.[1]



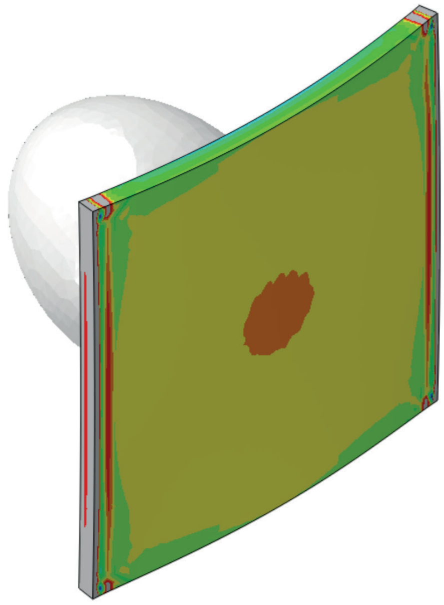


Figure 4: (a) Schematic of unit cell undergoing rotation at boundaries. (b) In-plane hoop stress showing approximately uniform tensile conditions with a local maximum at the centre. This region of greater stress is most likely to fail first, which is supported by experiments. The white ellipsoid is the gland beneath the flavedo.[1]

streams of droplets, losing all streamline velocity in less than 100 ms. The breakup of a coherent jet into a stream of droplets occurs within 2 mm of the zest surface.[1] In citrus jets we witness major-minor axis switching, a perturbation which is the result of eccentric orifices and one that encourages breakup. The orifice geometry through which citrus jets issue is often elliptical in nature, and at times shrouded by irregular edges of the torn zest. This rapid breakup allows the droplets to be advected easily and evaporate quickly.

DISCUSSION

The size of citrus oil reservoirs and the velocity of oil ejection result in large accelerations by jetting fluid.[1] Liquid at rest in the pockets is accelerated to velocities in excess of 10 m/s over the distance of ≈1 mm. Therefore, parcels of fluid in the reservoir will experience 5,100 gravities (g) of acceleration before exit, which is comparable to the acceleration of a bullet leaving a rifle. In nature, this acceleration is outdone only be the mantis shrimp at over 10,000 g and dung cannon fungus at 180,000 g but is perhaps unmatched in the plant kingdom.

Our results[1] and finite element investigations predict reservoir fluid pressures in agreement with simple fluid theory, but it would appear citrus fruits achieve a suboptimal configuration from the standpoint of achieving even higher pressures by not maximising the disparity between pith and zest stiffness. This material synthesis is likely limited due to the biological origin of the material. Therefore, the system leverages reservoir geometry for enhanced performance (high bursting pressure) indicating the observed elliptical geometries of the reservoirs. Such is a recurring theme in many biological systems where the limitations of material properties are overcome by the geometry or topology of the structure. In contrast, an outer layer with very low strength would not withstand the stresses associated with pressure rise in the small reservoirs and would thus rupture at lower pressures and produce slower, yet more stable jets. This indicates that synthetic devices mimicking citrus peels could be tuned to offer a wide array of jetting behaviours.

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FUTURE WORK

Now that the physics underlying citrus microjet production are well understood, we must explore synthetic materials which can be assembled into a citrus-like composite structure to perform, or even out-perform, citrus. This notion comes with challenges, but these could be readily overcome with the aid of partners in interested fields. Materials comprising a system mimicking citrus must possess an appropriate stiffness, thickness, be easily cut and machined and be chemically non-reactive.

The process by which two materials are joined will have a large influence on material fracture. Such fracture should ideally be brittle, as ductile fracture could allow cavity expansion and decreased performance. Material properties and desired ejection volume will drive reservoir volume, shape and packing fraction. An effective device must also achieve the desired droplet size distribution and dispersal distance, which are not mutually exclusive. By using stronger or thicker "zest" materials, we may generate higher fluid pressures, but will likely make jets break up more rapidly and have a greater distribution in droplet size. The spectrum of available materials will generate an assortment of orifice geometries, greatly influencing breakup.

Finally, it is critical we explore potential applications for this technology, which could reach asthmatics, the fragrance industry, dental hygiene, skincare and more.

ABOUT THE COMPANY

Headed by Dr Andrew Dickerson, the Fluids and Structures (FaST) Lab in the Mechanical and Aerospace Engineering Department at the University of Central Florida investigates the physics governing flow at the interface of fluids and deformable solids. The lab's research is inspired by natural systems and combines fundamental fluid and solid mechanics. FaST is excited to work with industry partners to commercialise the discoveries unveiled in the lab.

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ABOUT THE AUTHOR

Dr Andrew Dickerson is an Assistant Professor at the University of Central Florida and holds a PhD in Mechanical Engineering from the Georgia Institute of Technology. He is a fluid dynamicist with expertise in the mechanics of interfaces between fluids such as air and water, and a researcher in the biomechanics of animal locomotion. This research links areas of mechanical engineering, mathematics and biology to make an impact in medicine, robotics and conservation. His work has resulted in publications in a number of high-impact journals such as *Proceedings of the National Academy of Sciences, Journal of the Royal Society Interface, and Physics of Fluids.*

Over the years, his research has also played a role in educating the public in science and engineering. Dr Dickerson has been an invited guest on numerous television and radio shows to discuss his research, including Good Morning America, National Public Radio, The Weather Channel and Discovery Channel.