Sensors NSI Webinar Series

Advances in self-powered wearable sensors: A biofuel-powered electronic skin

June 24, 2020, Webinar

Speaker

Dr. Wei Gao
Assistant Professor of Medical Engineering,
California Institute of Technology

Webinar viewers will be able to submit questions for the panelists to answer during the Q&A period. Submitted questions will be considered in the order received and may be posted on the NNI website. A moderator will identify relevant questions and pose them to the speakers. Due to time constraints, some questions may be grouped and some may not be addressed during the webinar

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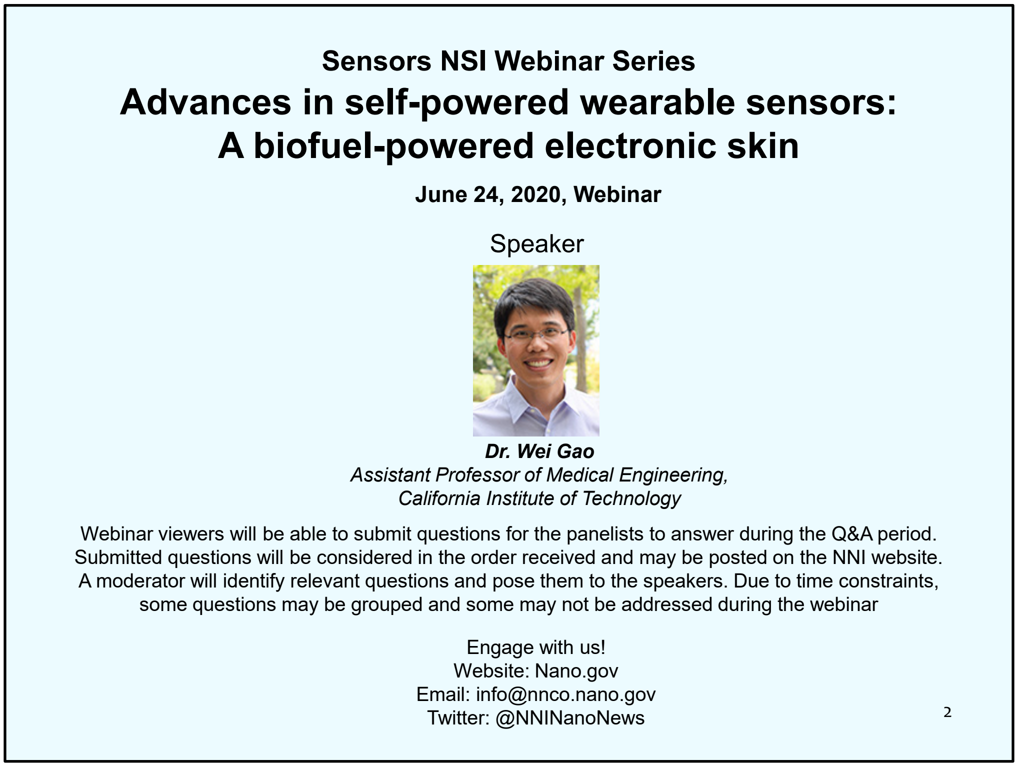
>> Stacey Standridge (NNCO): Good afternoon everyone. Welcome to today's public webinar presented by the National Nanotechnology Initiative, the NNI. Thank you for joining us. I am Stacey Standridge, Deputy Director of the National Nanotechnology Coordination Office. We are pleased to have as our speaker Dr. Wei Gao, Assistant Professor of Medical Engineering at the California Institute of Technology. Dr. Gao is the recipient of several awards, including the IEEE Sensor Council Technical Achievement Award, the Sensors Young Investigator Award, and the ACS Young Investigator Award. He is among the MIT Technology Review's 35 Innovators Under 35, a World Economic Forum Young Scientist, and a member of the Global Young Academy.

Today Dr. Gao will share his research on developing a biofuel-powered electronic skin. His work bridges innovation in material science, nanotechnology, engineering, and medicine to create novel bioelectronic devices for personalized medicine and synthetic micro/nanorobots for rapid drug delivery.



>> Stacey Standridge (NNCO): We are really happy to see that we had a record high number of registrations for this event today and a very diverse audience joining us. Before turning the webinar over to Dr. Gao, I wanted to say a few words about the NNI, which is the U.S. Government's R&D initiative involving the nanotechnology-related activities of 20 departments and independent agencies. If you have received Federal support for your nanotechnology research, you are a part of the NNI community, and we very much welcome your engagement. Among the efforts to support interagency collaboration, the NNI created several Nanotechnology Signature Initiatives, which we call the NSIs.

The Sensors NSI organized today's webinar to provide information on the challenges and recent advances in developing self-powered wearable sensors, which is definitely an area of relevance to agencies across the Federal government. So with that we encourage you to visit nano.gov for more information on the NNI and upcoming webinars or contact the NNCO at info@nnco.nano.gov. You can also follow us on Twitter, @NNInanonews. Dr. Wei Gao, thank you so much for your time today, and I'm happy to turn it over to you now.

>> Wei Gao: Thank you very much, Stacey, for that kind introduction. It's really my great pleasure to be here today to share my research on wearable sensors, especially our recent work on biofuel-powered electronic skin.

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A Biofuel-Powered Electronic Skin

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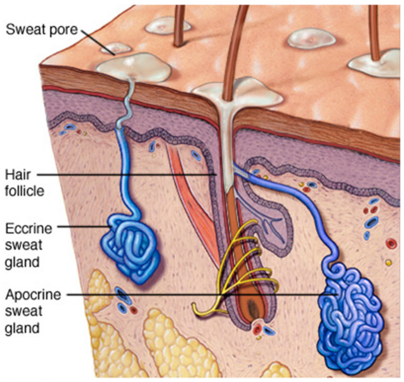
>> Wei Gao: Hi, everyone. As Stacey said, this is Wei Gao. I am an Assistant Professor of Medical Engineering at Caltech. To give you a bit of background, Medical Engineering is a new department at Caltech focusing on translational research. My lab is mainly working on developing devices—medical devices—especially wearable sensors for health monitoring.

>> Wei Gao: As many of you know or believe, wearable sensors will play a very important role in future personalized healthcare because they can continuously collect data from our bodies and tell us what is going on and what is going wrong with our health. If you look at commercially available health monitors like an Apple watch, Fitbit, or Samsung watch, right now there are many smart wristbands that can track different kinds of physical activities or vital signs. And many research labs are focusing on developing new vital signs monitors as well.

But we think the major challenge, one major challenge, which is also a great opportunity, is how can we collect chemical or molecular information continuously—and ideally, noninvasively—because right now commercially available health monitors cannot provide our health information at a molecular level.

Human Sweat



Electrolytes
- Na^+, Cl^-, K^+, NH_4^+, Ca^{2+}, H^+

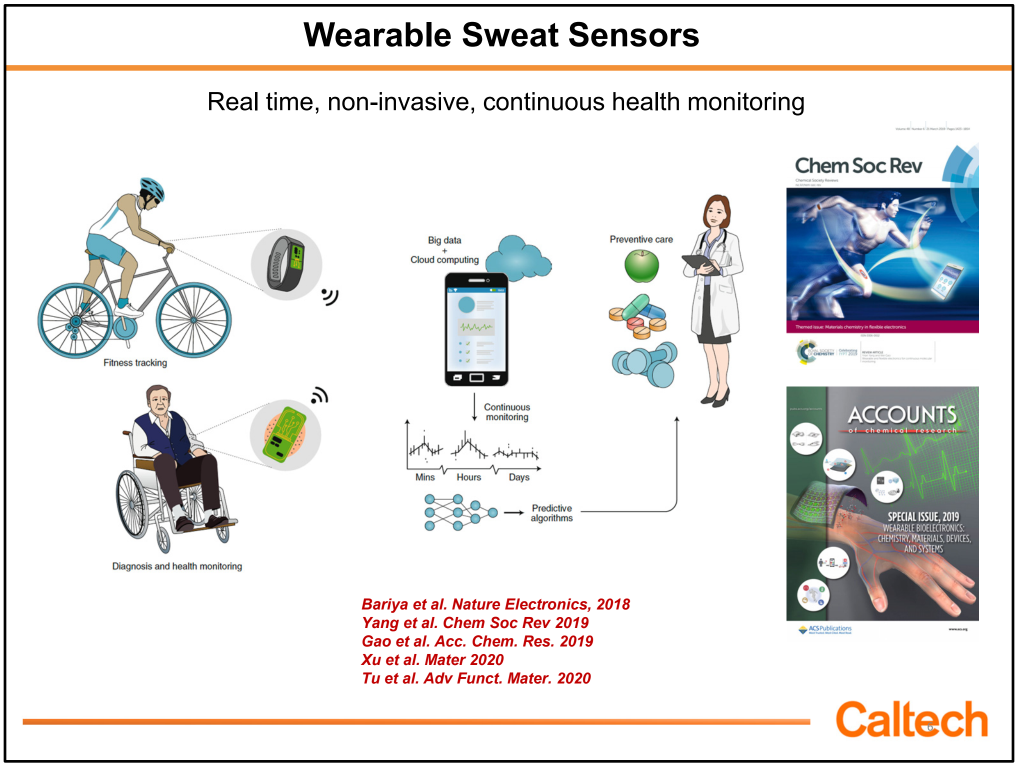
Metabolites
- Lactate, glucose, urea, uric acid, creatinine

Amino Acids, Vitamins, & Hormones
- Amino acids, Vitamin C, cortisol, DHEA

Proteins & Peptides
- Cytokines, TNF, neuropeptides

Xenobiotics
- Heavy metals (Cu, Hg, Cd, Zn, Pb)
- Ethanol
- Drugs

>> **Wei Gao:** In this regard, we are looking at human sweat as a promising fluid for developing a wearable sensor. Sweat is a very important fluid. It contains many important biomarkers, or analytes, including, for example, electrolytes like sodium chloride, potassium, and ammonium. It also contains many metabolites, including lactate, glucose, urea, uric acid, and creatinine. And we can find more than 30 amino acids and many common vitamins, hormones — actually, over 300 proteins. We can also identify different kinds of heavy metals or drugs from our sweat.

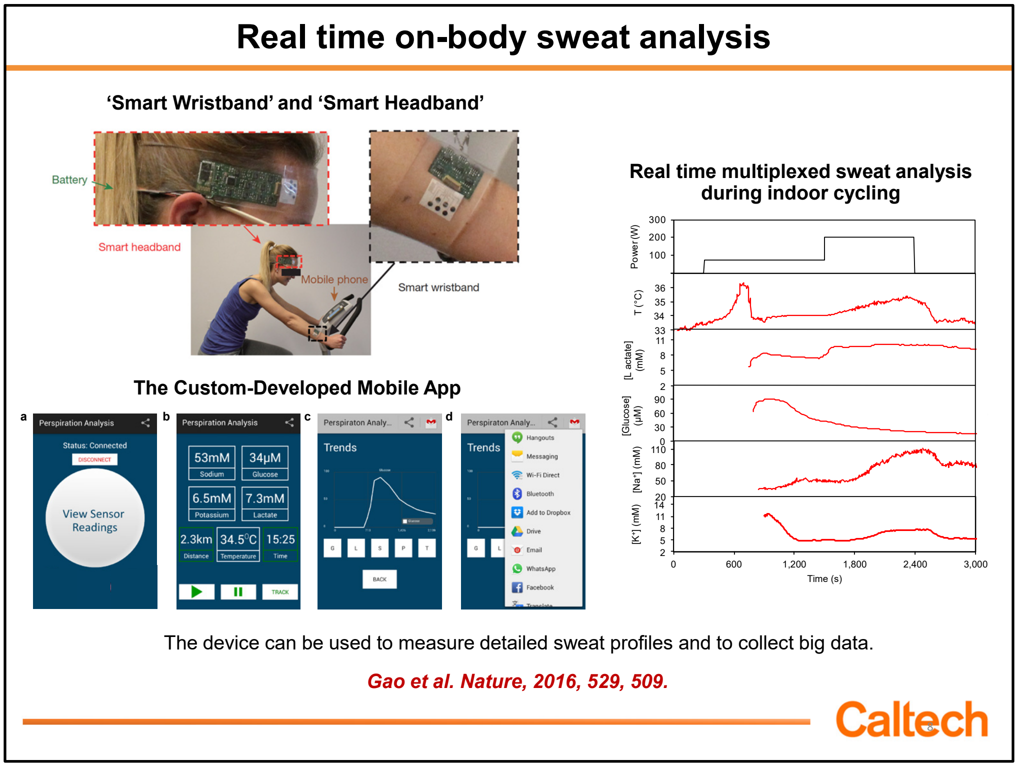


>> Wei Gao: Imagine if we could develop a wearable sensor, a wearable device, that can continuously collect this sweat information from our skin, we could potentially use this information for disease tracking or disease diagnosis. And, very importantly, the large sets of data collected by the wearable sensor, enabled by the wearable sensor, when coupled with different kinds of data algorithms, machine learning, we can use this information for numerous fundamental and clinical investigations, for example, preventative care, preventing or minimizing the risks of developing major health problems. We have a few peer-reviewed articles published recently; if you are interested, you are welcome to read.

>> Wei Gao: In 2016, we developed our first-generation wearable sweat sensing platform. As you can see, here is a fully integrated system rather than only a sensor patch. It contains not only the sensors but also signal processing circuitry, wireless communication, and even the cell phone app. Basically, we built a protype. This device can real-time monitor several different kinds of sweat biomarkers, including glucose, lactate, sodium, potassium. We could also monitor skin temperature for real-time signal calibration.

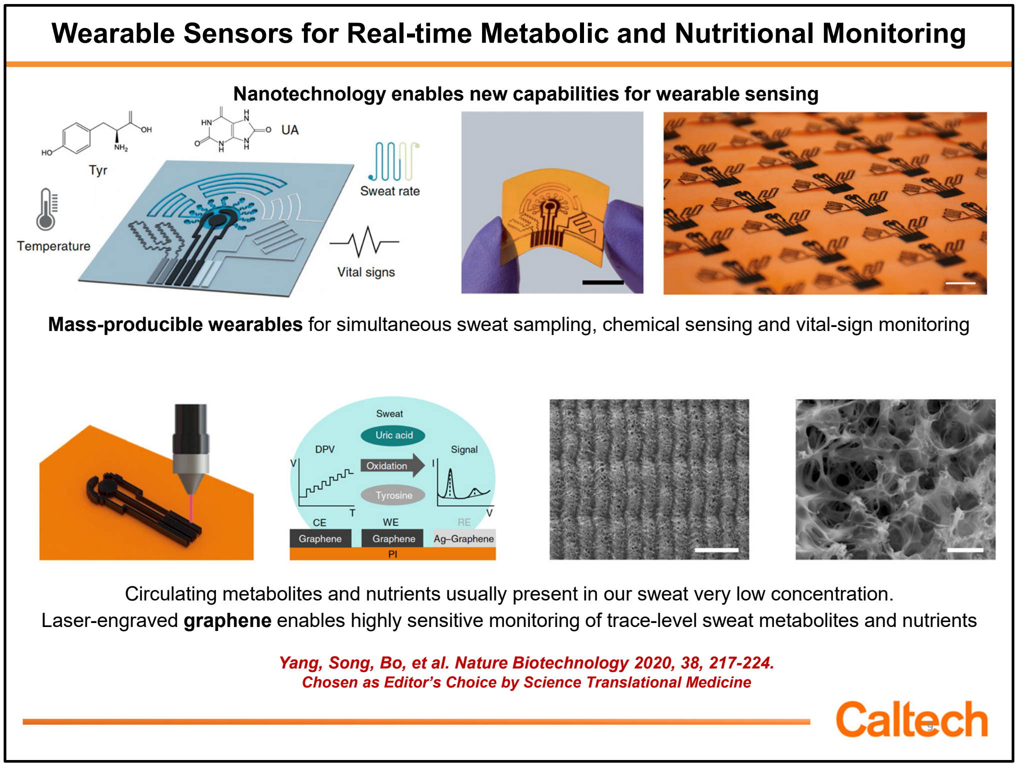
Basically, the system can perform on-site, from the skin, signal processing for wireless transmission; the data will be sent to a cell phone, to Bluetooth, and displayed in a custom-developed cell phone app. We can save the data to the cloud for later analysis. Since then, our lab has developed different kinds of prototypes of wearable sensors that could be used for many applications, as you can see from this slide. These are example prototypes, with different purposes, all analyzing sweat.

I want to mention that you might think about a sweat sensor, “I don't sweat; would this device be useful?” That's a good question. We have an interesting approach. I don't have time to say too much today, but I want to mention that we can use this wearable wristband or sweat sensor to induce sweat on demand. In this case, you don't have to exercise; you can get sweat continuously only from the wristband area.



>> Wei Gao: When we place this device into a wristband or headband, or different kinds of wearables, like a phone, we can use this device for continuously collecting data from our body. As you can see, this is one representative curve, basically collected from a subject during vigorous exercise. During the time, you can check all the values of the target analytes from your cell phone, from your mobile app. We developed an Android app, and now we have a new iOS version as well. You can check the progression profile of each analyte. Eventually, you can save the data in the cell phone or send the data to the computer through e-mail. This large set of data collected from the skin can be used for numerous applications.

In the following few slides, I will show you a few examples where we can use this wearable sensor towards personalized healthcare.

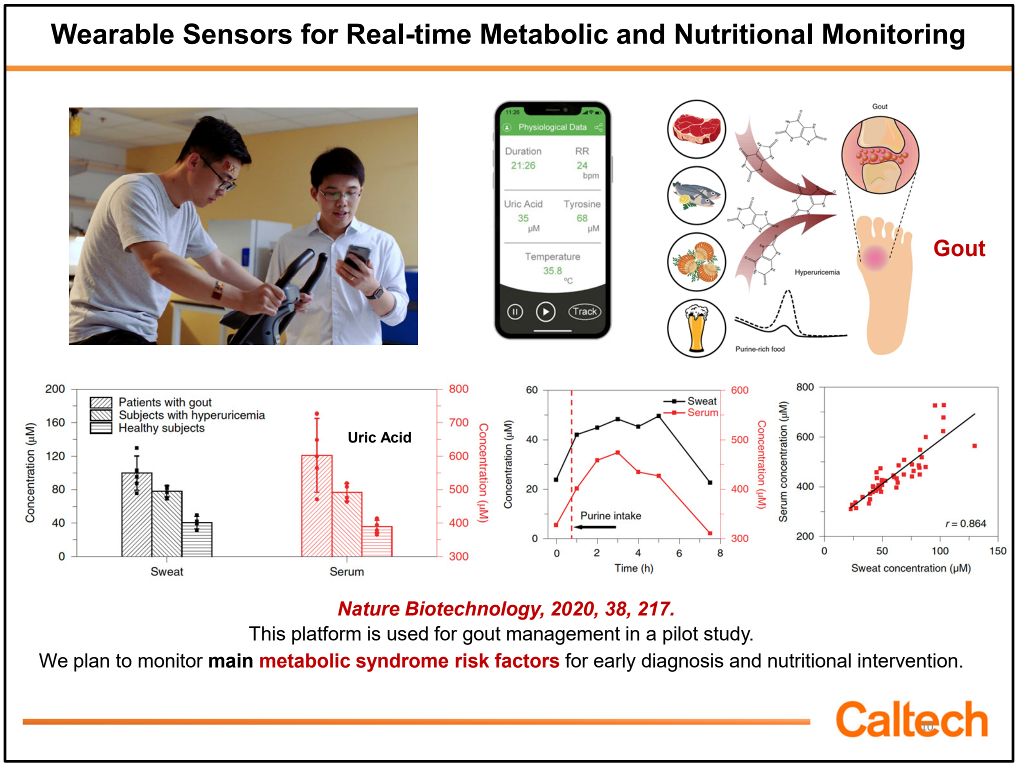


>> Wei Gao: The first example I want to show you is using wearable sensors for metabolic and nutritional monitoring. As we know, circulating metabolites and nutrients are closely related with our health. The normal levels of these nutrients and metabolites actually relate to different health conditions. Common examples are glucose for diabetes and uric acid for gout. Many of these biomarkers are related to different health conditions. But most of the metabolites and nutrients are present in our sweat at very low levels. So sensor development is very critical in this case.

We developed, basically, a laser-engraved approach, which allows us to develop this graphene-based biosensor that can perform real-time sweat analysis at trace levels. For example, as you can see, this beautiful graphene structure is just fabricated using laser engraving on a simple polyimide structure. Using laser engraving alone, we can make this whole patch that can monitor vital signs, be used as a chemical sensor, and we can also use microfluidics to minimize the influence of the skin contamination and the sweat evaporation to get an accurate signal.

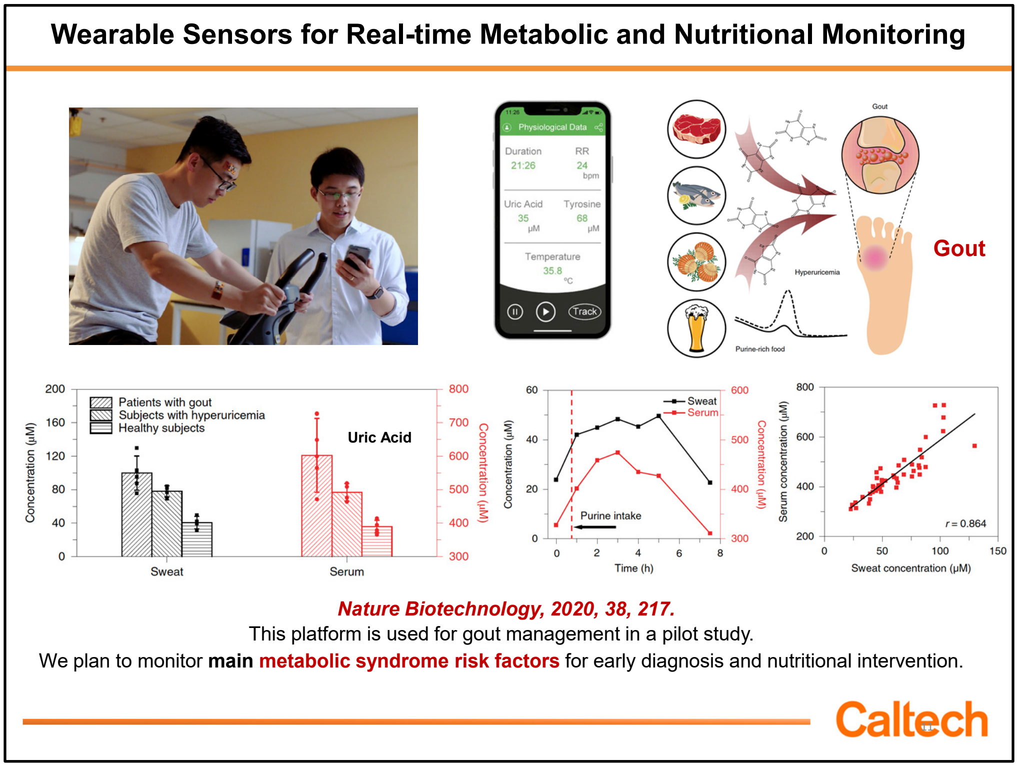
The use of nanotechnology here is very critical for us to detect the trace-level, micromolar-level or even submicromolar-level, nutrients and metabolites.

This paper, published earlier this year in *Nature Biotechnology*, was featured as Editor's Choice in *Science Translational Medicine.*



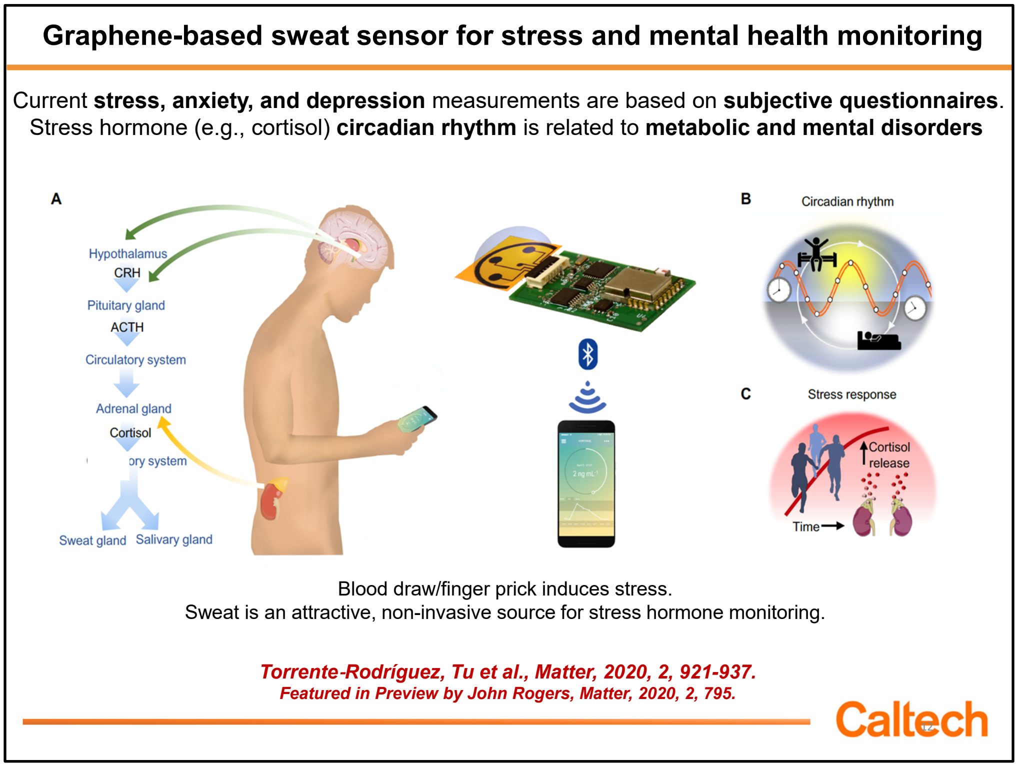
>> Wei Gao: This is one of my students; he is wearing this device on his wrist and forehead. We can get the data from the cell phone. You can see during the exercise we continuously collect data. In one example application, specific application, we used gout as a target health condition. Gout is a very important health condition that affects millions of people around the world. Even my brother has gout. You should not eat rich food such as red meat, seafood, or beer. It's very painful for the patient when they have a gout attack.

The patient who has a history of gout would love to monitor their uric acid levels to prevent or minimize their risk of a gout attack. The kind of patient who is on medication for gout at the low end of uric acid therapy will prefer to monitor uric acid levels to control their diet and control their medication, as well, because medication levels that are too high or too low are both harmful for patients. (*cont.*)



>> Wei Gao: (*cont.*) We conceived a study where we recruited a patient with gout, a subject with hyperuricemia, as well as a healthy subject. We analyzed the sweat uric acid levels using our sensors and analyzed the serum uric acid using HPLC (high performance liquid chromatography). We found a very high correlation between sweat and serum uric acid. We monitored one subject over seven hours continuously. As you can see, the sweat biomarker, sweat uric acid, follows the serum level very closely. When we put our data together, we found a very high correlation factor of 0.864 between sweat and the blood uric acid. This is just a proof-of-concept example showing how sweat analytes could reflect blood ones. Monitoring sweat analytes noninvasively could enable continuous metabolic and nutritional monitoring.

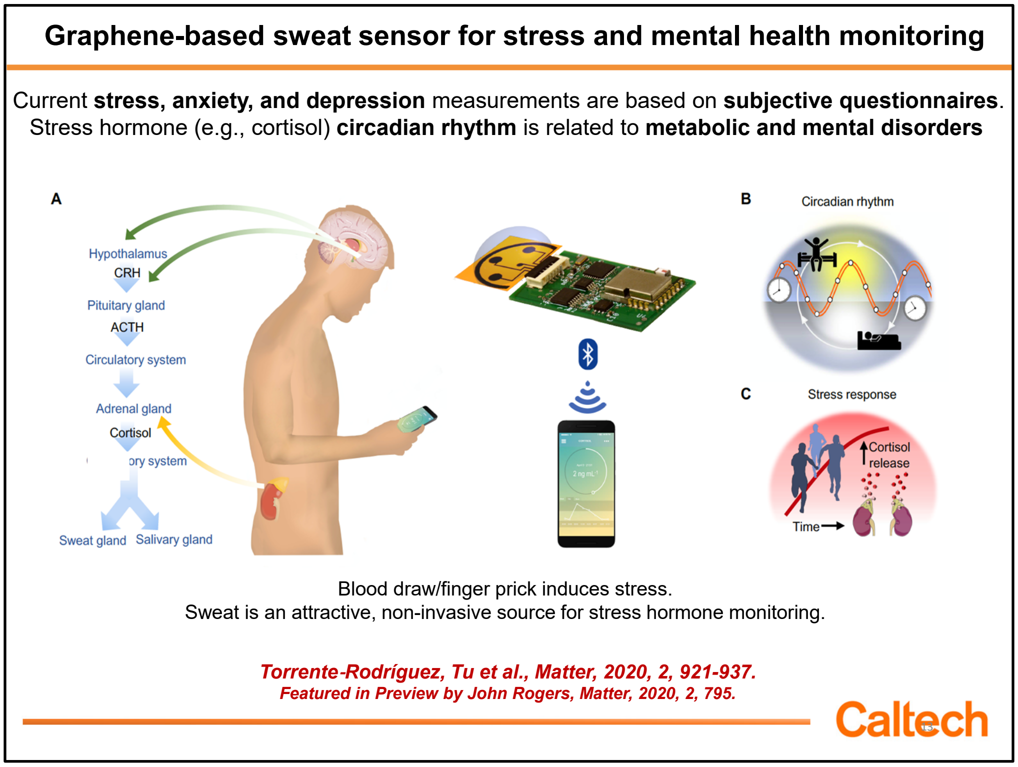
We're currently working closely with UCLA Medical Center to monitor patients with different health metabolic conditions for metabolic syndrome. Eventually, this device could be used for preventing the development of these metabolic disorders through nutritional disorders, because this information collected by the wearable sensor will give the subject, it will give the user, information to tailor their diet. It is very important to prevent the development of disease.



>> Wei Gao: The second application example I want to show you is also a very important topic. Can we use a wearable sensor to monitor stress, to monitor depression, and other mental disorders? Stress is a very important health condition that basically could lead to mental disorders like depression and PTSD. Stress is also very related to human performance.

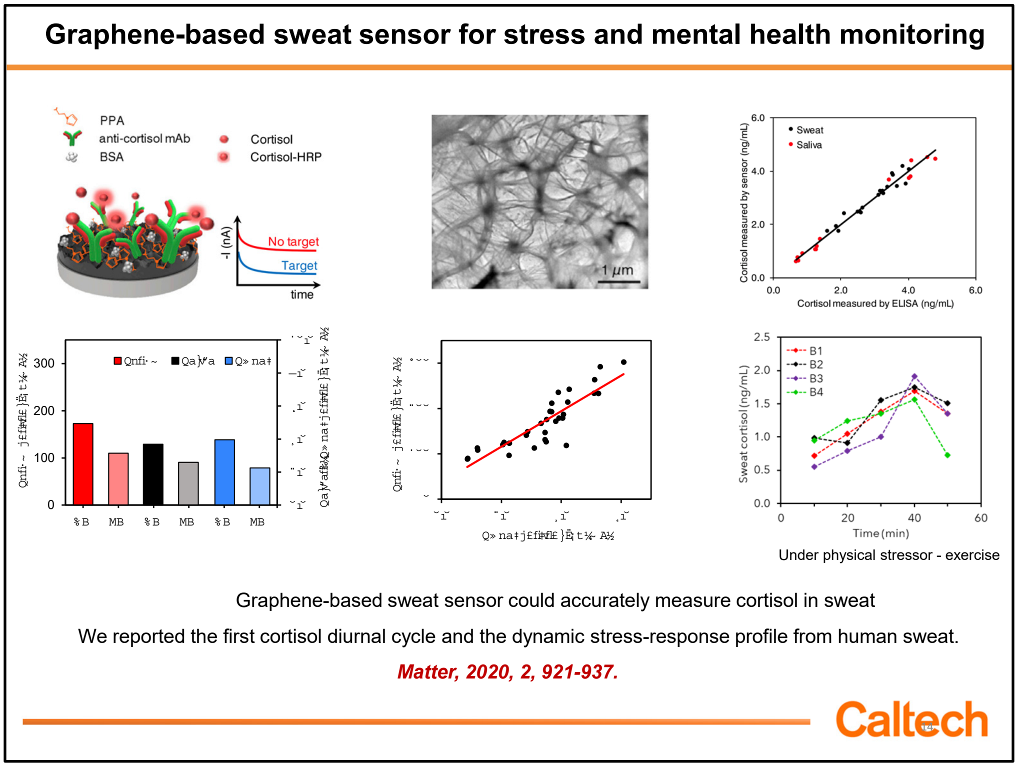
How to monitor stress clinically? The gold standards for stress analysis, they are based on questionnaires. Basically, we give a bunch of questions and based on your answers, we get your stress levels. As you can imagine, the answers could be very subjective. Depression is similar. Major depressive disorders are affecting hundreds of millions right now around the world, at least 250 million around the world. I think with COVID-19, people are even more likely to have PTSD right now. It already affects 6-9% of the U.S. population even before COVID-19. So, they're all based on questionnaires, subjective.

The question that comes to us is, really, can we use our sensor to quantify this stress or depression level? Right now, one of the most important biomarkers for mental health is stress hormones like cortisol. When we are stressed out, cortisol levels increase in our bodies. People try to analyze the cortisol level by a simple blood test, but as you can imagine, when you take blood, finger pricks or blood draws, the process itself causes a lot of stress. That makes your data of cortisol in blood not accurate. (*cont.)*



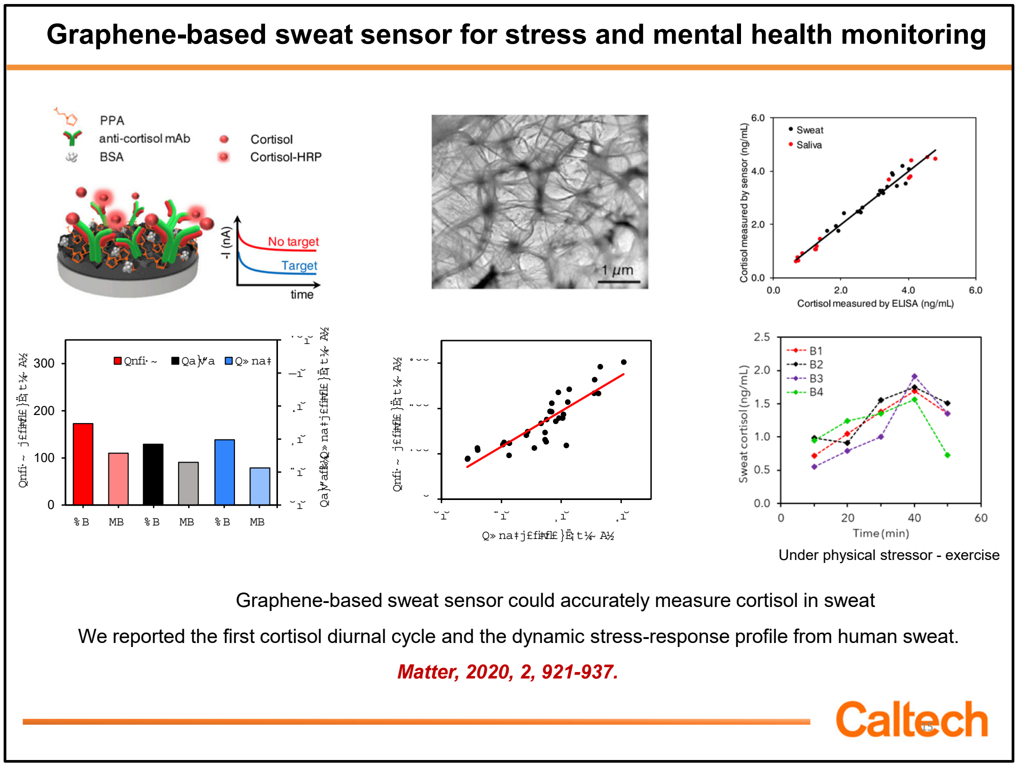
>> Wei Gao: (*cont.)* So, can we use our wearable sweat sensor to monitor stress or mental health? Recently, we developed one such platform, a mobile health platform that can noninvasively analyze cortisol from your skin.

I want to mention that the cortisol level is important. The cortisol in a patient over a day is also very important. Because the circadian rhythm of the cortisol is informative for depression and metabolic disorders. For example, the depressed population has a different kind of circadian rhythm compared to healthy subjects. Typical cortisol is high in the morning and low in the afternoon.



>> **Wei Gao:** Using our graphene-based biosensor, we've developed a highly sensitive cortisol monitor. We can monitor saliva cortisol; we can monitor sweat cortisol. The cortisol level measured by the sensor has a very high correlation with ELISA (enzyme linked immunosorbent assay, the U.S. gold standard way to measure cortisol). We found both sweat and the saliva cortisol levels had a very high correlation compared to serum. I believe the correlation factor also is around 0.87, based on sweat and serum cortisol levels. This shows that we could potentially use a wearable sensor for noninvasively monitoring the stress hormone to monitor stress.

We did a human study to verify if we can use our device to monitor the stress dynamically. We performed the human study and we applied different stressors to the subjects. Here is one example: we used a physical stressor, exercise. When you do exercise, basically you are stressed out. You can see the cortisol level increases during exercise and decreases after exercise. (*cont.)*



>> Wei Gao: (*cont.)* We also did other stressors. In one, the subject puts his hand into ice water; the subject will feel pain. This pain creates a lot of stress. You can monitor this stress level continuously, as well, using our device, without exercise. I was lucky to be the first subject for our study. At least I wanted to try how I felt about this study before we recruited real subjects.

While I put my hand in ice water, all my lab members were looking at me and making me even more stressed, because I felt it was really painful for a minute. Eventually, I knew why they were looking at me. I found everyone had put in one dollar—they just tried to bet how long I could keep my hand in the ice water. It was a fun experience. Eventually our device showed that we can rapidly capture the dynamic changes of this stress hormone in sweat. So this is another application of using wearable sweat sensors.

Considerations for designing future wearables

Communication – continuous and wireless data transmission

Power – sustainable power supply

Sensors – highly sensitive and selective biosensing

Applications – personalized health monitoring and diagnosis

Caltech

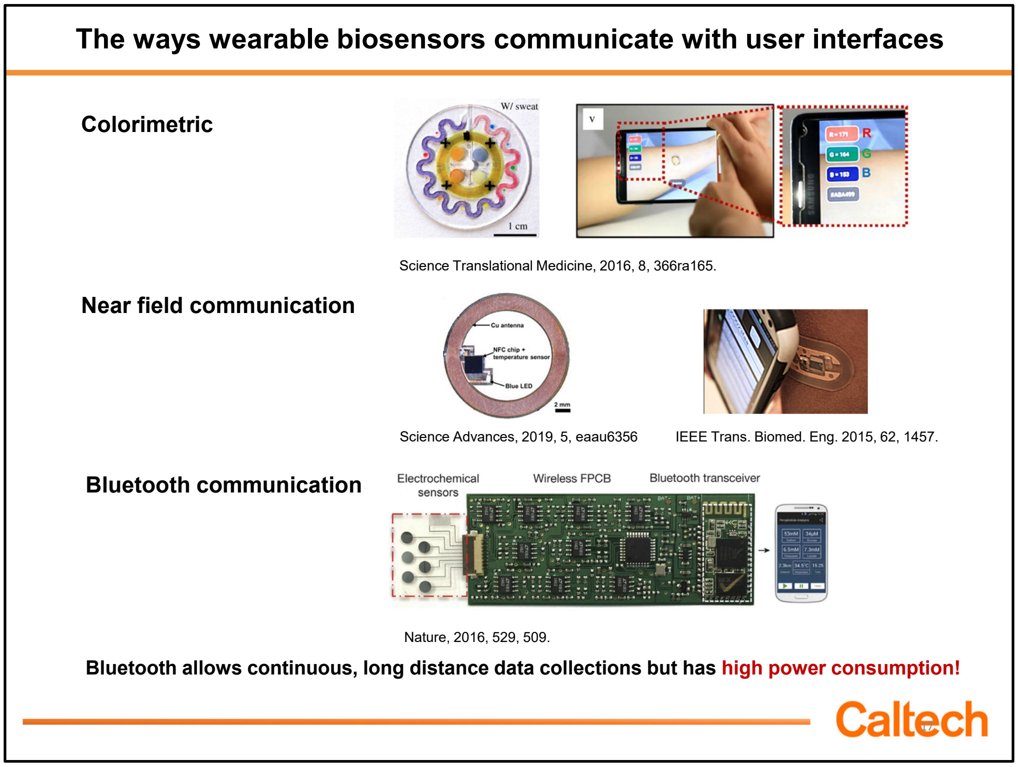
>> Wei Gao: I showed you some promising applications of wearable sweat sensors. We're actually working on many more topics. For example, we could use sweat sensors to monitor therapeutic drug levels to achieve drug personalization in the future for precision medicine.

Here I want to talk a bit more in a different way. What are the main considerations for designing future wearables? There are several aspects I put here, including *communication*, *power*, *sensors*, and *applications*.

In the case of the sensors, I already showed you some examples of how we use nanotechnology and nanomaterials to really enable continuous monitoring of trace levels, very low-level biomarkers from the skin. For applications, of course, for all the wearables, we need to find the killer applications. I showed you some potential applications using our wearable sweat sensor for metabolic monitoring and for stress/mental health monitoring.

So, the first two are also very important, and I want to emphasize *communication* especially. How can your wearables interface with the user, and how can we get the data from wearables? Ideally, we want continuous and wireless data transmission.

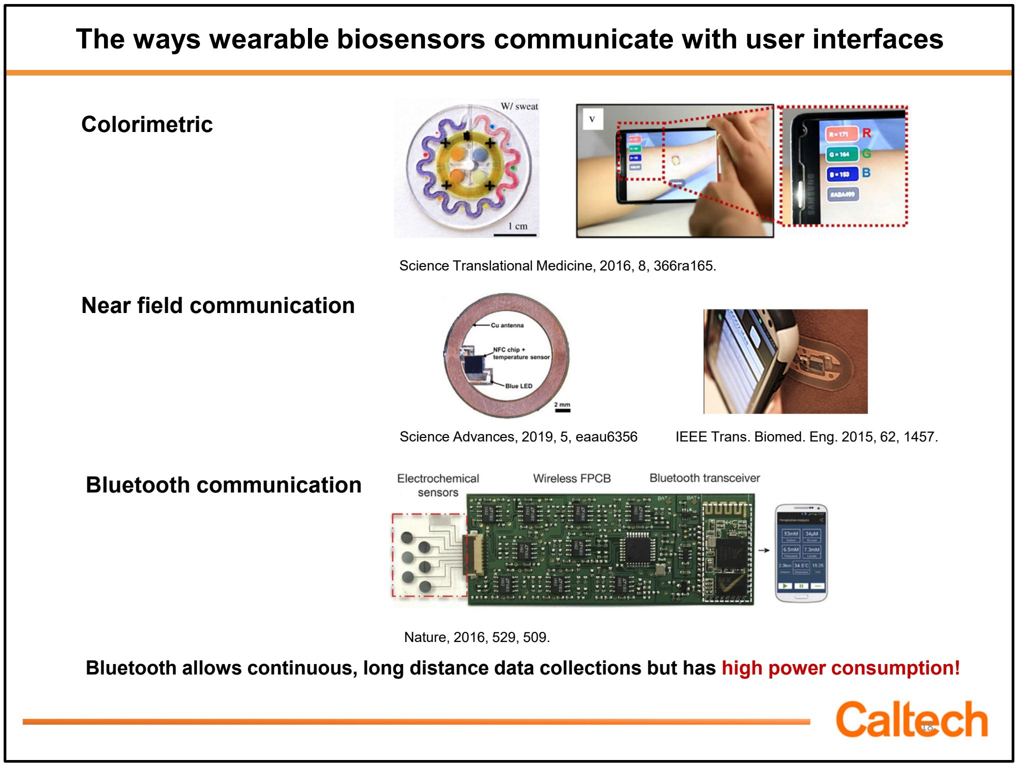
The second part is *power*. For all the wearables, when we have more functionality and we want powerful performance, we need higher power also. How can we sustainably power our wearables? It's also a very important aspect.



>> Wei Gao: In the case of communication, what are the common ways right now that wearables are communicating with the user interface? Here I summarize the field.

A colorimetric one is a simple approach. Basically, with this design, a sensor, using a calorimetric sensor, is an optical sensor. When the sensor is working, it displays different colors for different levels of analytes. An example of this work is a sweat patch developed by Professor John Rogers now at Northwestern University. This patch can monitor glucose, lactate, chloride, and pH. When you have different levels of the target, this patch shows different colors. We can use our eyes to see the color changes. To get high accuracy, you could use a phone to take pictures to analyze the RGB component of each sensor, and get a rough level of your target analyte. This approach is very simple. But it's also problematic because you only get, effectively, a disparate point. Meanwhile, if you take a picture, you can get this measurement. If you don't get a picture, you don't get a measurement. The data is not continuous.

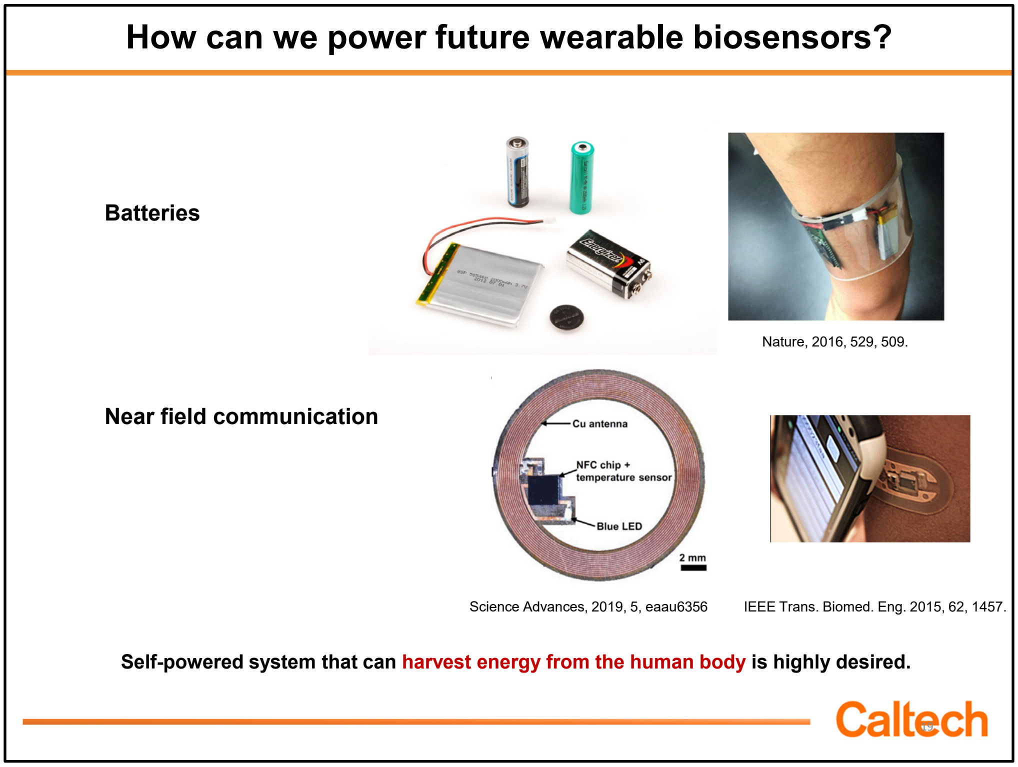
Another promising approach is near-field communication. Basically, you have this antenna that can wirelessly communicate with a phone. It's pretty simple because this one can also serve as a power source; the phone can power the device through near-field communication as well. In the meantime the phone can get data, but the limitation is you have to put the phone very close to the device, like this. (*cont.)*



>> Wei Gao: (*cont.)* If your phone is not super close, you don't get a signal, you don't get a measurement. That is also a problem. It means in regular activity you don't get a measurement; you also get an isolated point.

Bluetooth communication. It's one of the most promising communication methods for wearables. Basically, right now, nearly all the smart watches like Apple Watch, Samsung Watch, they communicate with your phone through Bluetooth. We are using Bluetooth every day while we transfer files from the phone, from the computers. It's a very promising approach that allows continuous long-distance data collection or data transfer.

I think Bluetooth is probably the most promising way for wearable communications, but the problem for Bluetooth is it consumes high power. It gives higher power requirements for your design of the wearables.

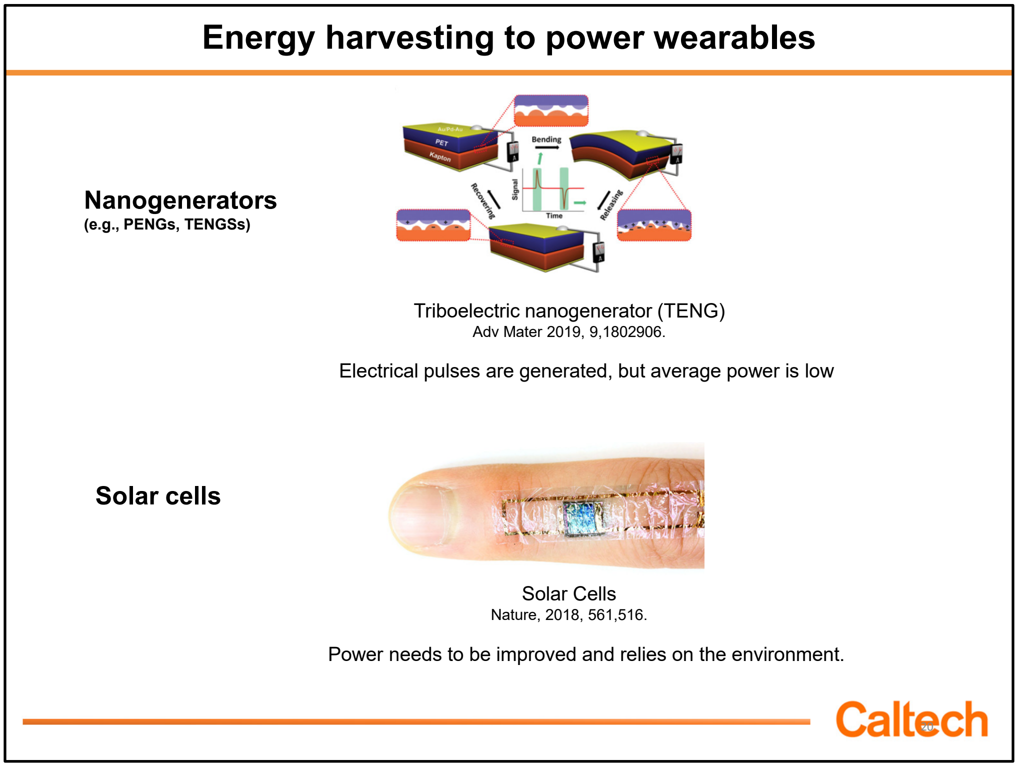


>> *Wei Gao*: Now that we're looking at power supply, how can we power our wearables? As you can see, typically, nearly all the wearables right now, they're using batteries, the different type of batteries that we we can find in our everyday life. This is from my own work. We use a small lithium battery here to power our wearables.

The battery has its own problems. Firstly, the safety of the battery is one consideration, and also, battery electricity can run out, right? You can say, I can recharge my battery, but basically, in many scenarios, electricity for recharging is not readily available. In this case, people cannot recharge the battery in some places or in some scenarios. Then how can we power the devices?

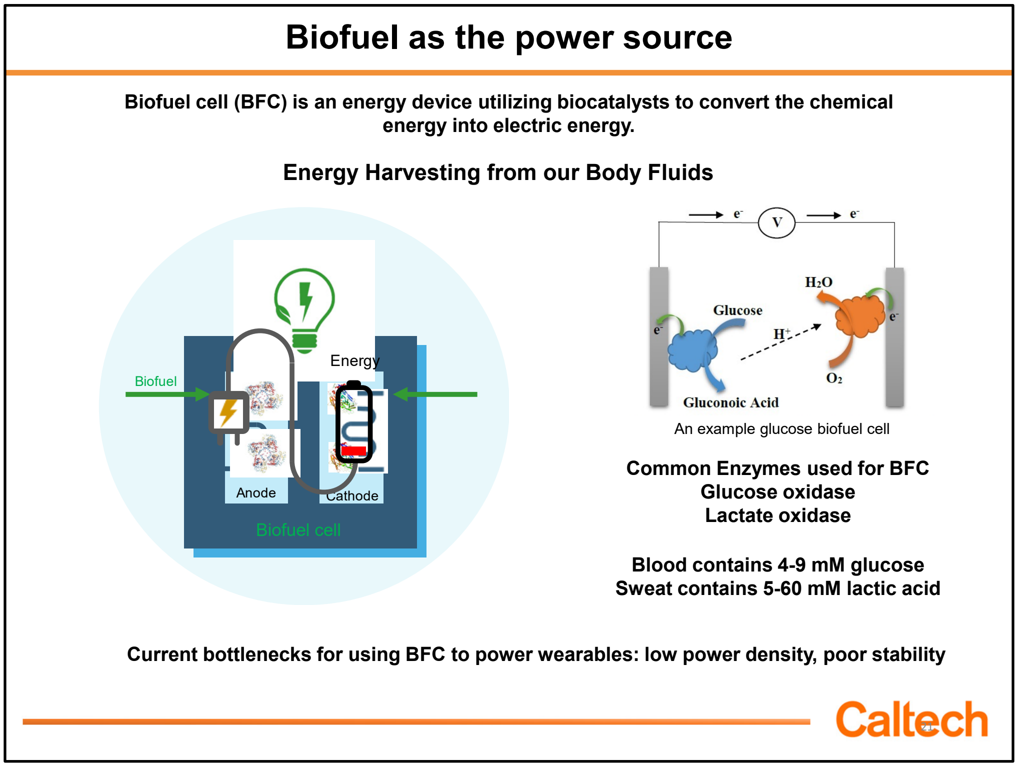
As I mentioned in the previous slide, near-field communication can work not only for data transmission, it can also serve as a way for powering the device. Basically, you can use the phone, when you put your phone close to the device, you can use near-field communication to power the device as well.

But again, the problem is the same: you have to put your phone very close to the device to get the data to power the device. So, in this case, you can imagine, if we could develop a self-powered system that can harvest the energy from our body or from our surroundings, this type of system is highly desired.



>> Wei Gao: If we look at what we have here right now, many people are working in this field for self-powered sensors. If you look at the literature, you would find different sources. For example, people developed, especially Professor Zhong Lin Wang from Georgia Tech, who pioneered the nanogenerators. Now, many people look at this topic. Basically, using piezoelectrical nanogenerators (PENG) and triboelectrical nanogenerators (TENG), you can harvest energy from your motion, from pressure. In this case, no matter whether PENG or TENG, there are basically generating electrical pulses. For example, for TENG, you have sliding between two electrodes, you can generate an electrical pulse; you could generate high voltage. From piezoelectricity, the same thing. You have electrical pulse and high voltage, it has high voltage, but overall, it's just pulses. Average power over time is pretty low. It's generally not sufficient to power Bluetooth. Of course, this needs more innovation to increase the power density, for example.

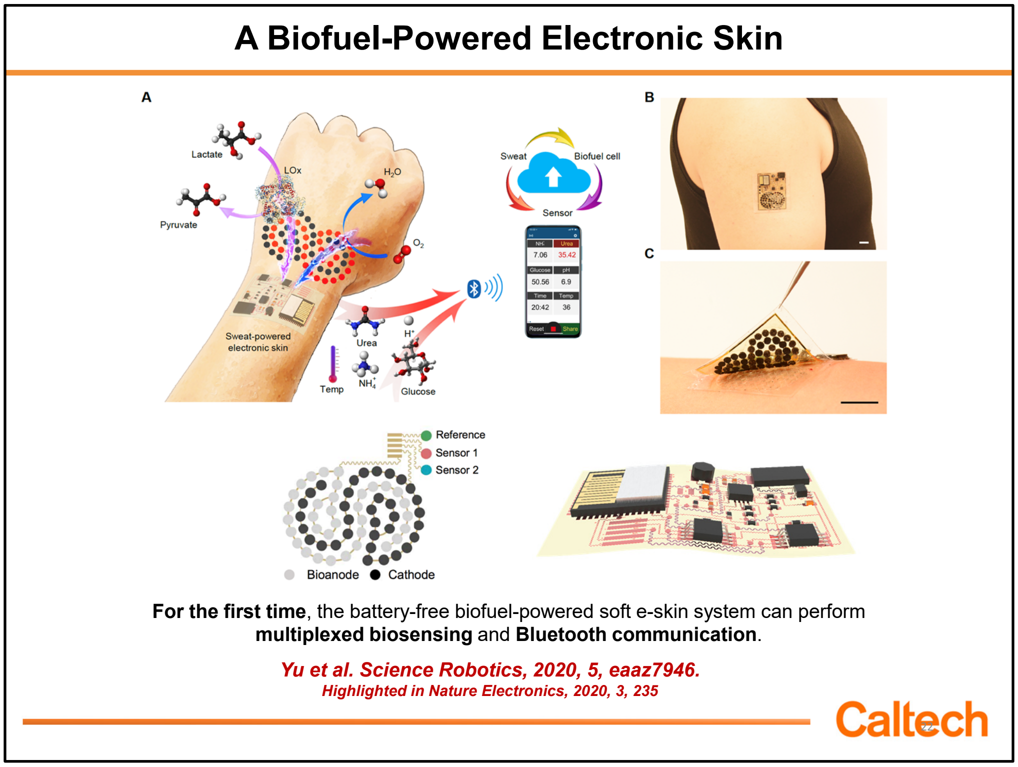
Another promising approach is solar cells. Many people are developing solar cells. Solar cells could harvest energy from the sun, and we can use this solar cell to power our wearables. This article from Prof. Takao Someya describes using wearable sensors to power the vital signs monitor. But again, the power needs to be improved, especially if we want to use Bluetooth communication. And solar cells also have limitations. If you want to use it at night, it's not accessible; we cannot get enough power without strong light. Now the question comes to us, can we really harvest energy from our body more efficiently, for example, using biofuel?



>> Wei Gao: Basically we come to an important concept, a biofuel cell. A biofuel cell is an energy device that utilizes a biocatalyst to convert the chemical energy of our body into electricity. Basically, this biocatalyst, in most cases, is an enzyme. For example, we could use glucose oxidase to harvest energy from glucose. We could design lactate oxidase biofuel cells to harvest energy from lactate. Our body fluid contains high levels of glucose and lactate; our blood contains 4-9 millimolar (mM) glucose. Our sweat contains even higher lactate levels, 5-60 mM. So it would be great if we could develop a biofuel to directly harvest energy from the skin, from sweat. Especially—we are doing sweat sensing, right, we need sweat anyway—why not harvest energy to power the device using sweat?

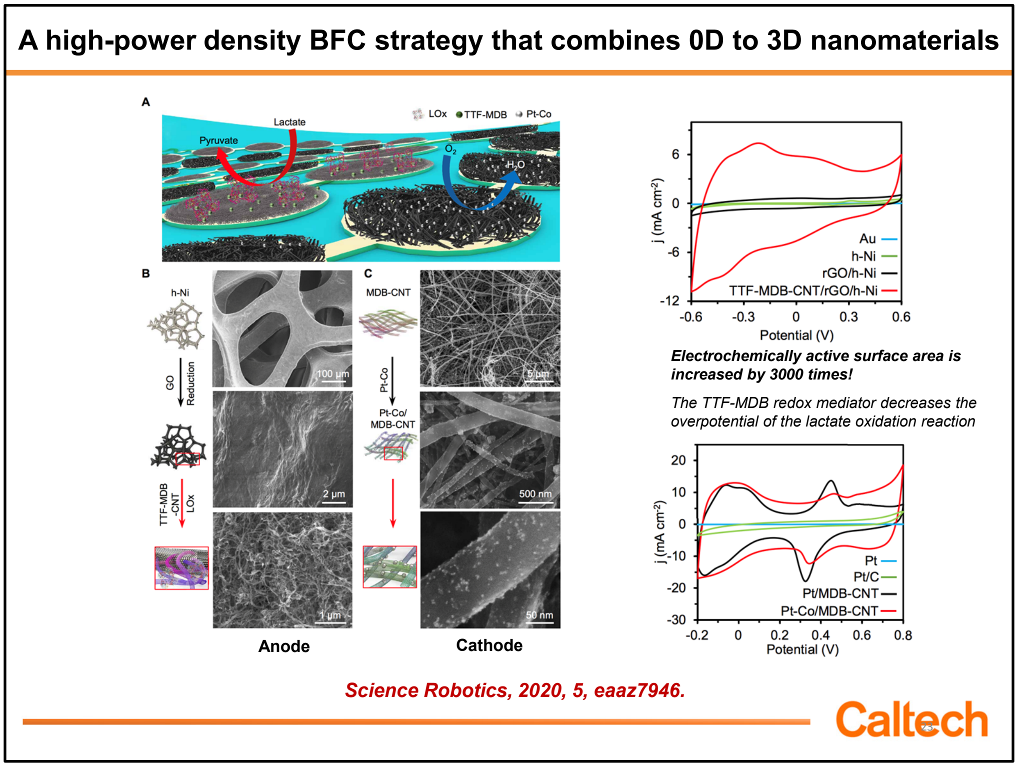
To give you a concept of how a biofuel cell works, just using common glucose biofuel cell as one example… One biofuel cell has two electrodes. The left side is the anode, the right side is the cathode. On the anode side, we can mobilize the enzyme here. Basically, at the two sides, anode, cathode, there's an oxidation-reduction reaction. Glucose, this enzyme, for example, catalyzes glucose. The oxidation reaction happens at the anode, glucose becomes gluconic acid. If we use a platinum cathode, the oxygen would be reduced to water at the cathode. When this oxidation reduction reaction happens at both electrodes there is electron flow between the electrodes, and in this case, we get electricity.

So biofuel cells seem pretty promising for powering wearables. But there are also bottlenecks for biofuel cells. Because typically they cannot provide sufficient power, and one of the major problems is they have poor stability because of the chemistry design. The electrodes have poor stability over time using body fluids.



>> Wei Gao: So, we have to address this problem, right? Very recently, I think two months ago, we published our work, You Yu et al. We designed a biofuel-powered electronic skin that can harvest energy from sweat using sweat lactate and power fuel cells, and we can design a system that powers multiplex biosensing and performs Bluetooth communication at the same time. This is the first time we could achieve this, actually, people could achieve this, using a battery-free biofuel-powered system for biosensing and Bluetooth communication.

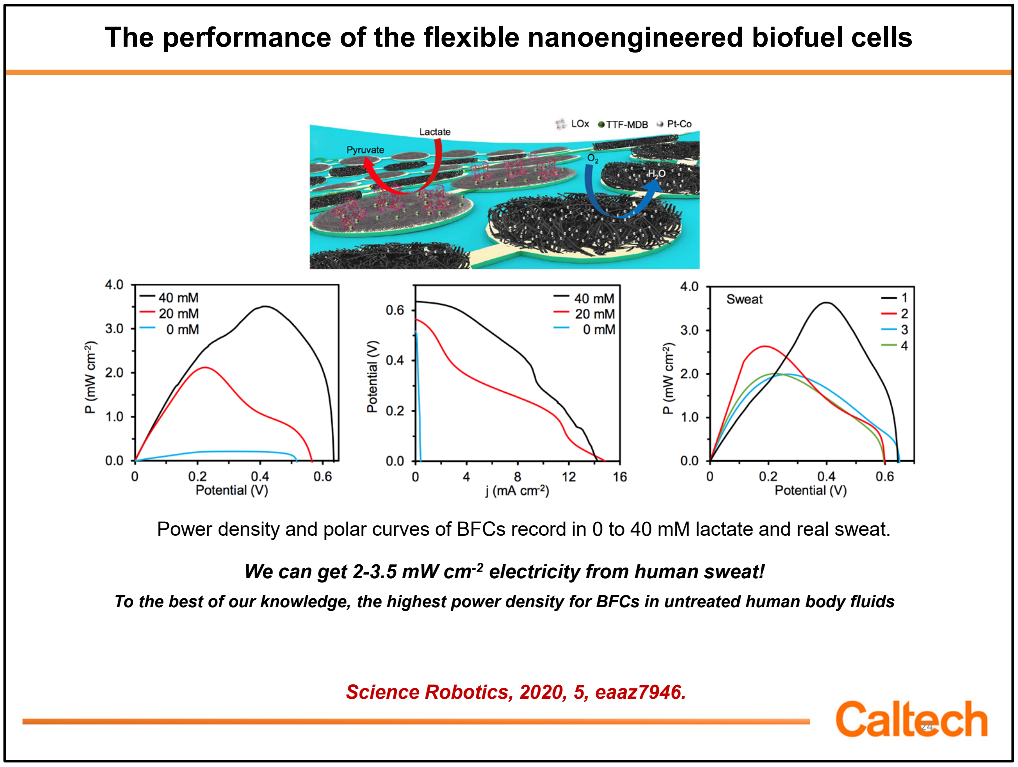
Why can we achieve this? It's a great achievement because it means that we have had to address the previous challenges: how can we get superhigh power, and how can we use this for a long time in the body fluid? The paper appeared in *Science Robotics* and was highlighted in *Nature Electronics*.



>> Wei Gao: So, the reason we could make this breakthrough is, again, nanotechnology and nanomaterials. We did innovation in our electrodes, anode and cathode, as you can see here. As I mentioned earlier, the anode has an oxidation reaction and lactate gets converted to oxide because of the presence of this lactate oxidase enzyme.

So we actually did a nanomaterial modification in our anode where we used a 3D microstructure, starting with the 3D structure, and we can coat the graphene on the 3D microstructure. On top of the graphene we actually immobilized carbon nanotubes. The π-π interaction between carbon nanotubes and graphene enhanced the electronic transfer and through this nanomaterial modification, we increased the surface area of the anode by 3000 times—the electroactive surface area—the most useful parameter for designing biofuel cell anodes.

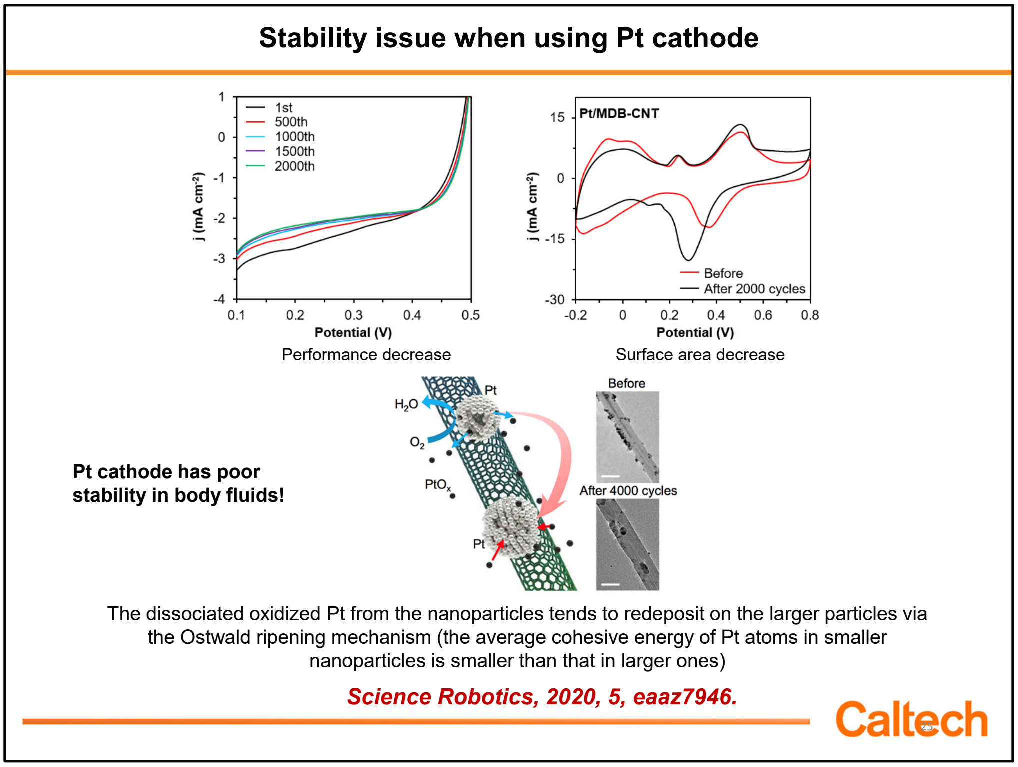
We also used this TTF-MDB (tetrathiafulvalene-Meldola's blue) redox mediator to lower the operation potential to decrease the overpotential of the lactate oxidation reaction; in this case, the oxidation reaction happens at very low voltage. On the cathode side, we also did a proper immobilization. We started with a carbon nanotube film. We decorated the carbon nanotube with nanoparticles--platinum nanoparticles or cobalt nanoparticles--this also increased the performance of the cathode by hundreds of times.



>> Wei Gao: So, combining this nanoengineered cathode and nanoengineered anode, we actually get record-breaking power for the biofuel cell, as you can see. If we test this in lactate solution, 20 millimolar, 40 millimolar, we get 3.6/cm^2 millibars. You look at the polar curve, the operating voltage, we can get very high power, actually.

Basically, you can see, we tested human sweat, as well, because this is something we really care about. We want to use sweat to power our device. We care about the performance of the biofuel cell in human sweat.

So here are four examples of sweat samples we analyzed. We actually tried to put our biofuel cells in these samples: we got from all of these as high as 2 millibars/cm^2; in one subject we even got 3.5 millilbars/cm^2. This is by far the highest result for any biofuel cell power in what we test this for, in human body fluid. Several millibars per cm^2. This is a huge progress in terms of designing human wearables.

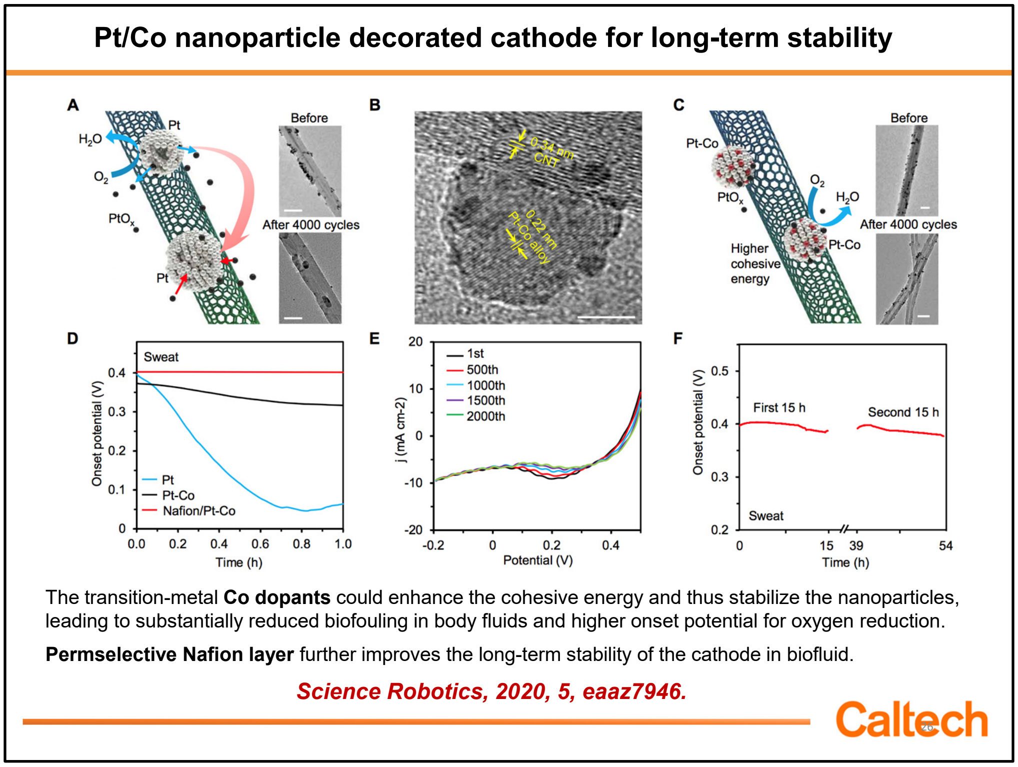


>> Wei Gao: We get high power by using nanomaterial modification. But we need to also address another problem, stability. I mentioned earlier that stability is one of the bottlenecks for biofuel cells. Here I want to show you why. Whenever you use a platinum cathode, particularly when you keep scanning your electrodes, for 1 time, 500 times, or 2,000 times, you can see that your power density or performance decreases over time when you use platinum cathodes.

If you keep scanning the CVs, the surface area, let's look at from negative 0.2 to 0.1, this is the hydrogen adsorption area**.** Initially, it's a red curve. After we scan, it basically becomes a black curve. The surface area significantly decreases after you use 2000 cycles. That's actually the performance of a typical platinum cathode. Poor stability. The reason is platinum, even though reasonably stable (in some cases), is not that stable (for wearable use). Platinum can be oxidized, and oxidized platinum will get deposited onto a larger particle because the average cohesive energy of the smaller particles is smaller than that from the larger particles.

Before we do a study, we see many small particles, but after we do a study, we see fewer small particles and we see only a few larger particles. That means the surface area changed. Actually, the nanoparticle island in the carbon substrate has a higher electromechanical performance.

In this case, the stability from this data is pretty poor. How can we improve it?

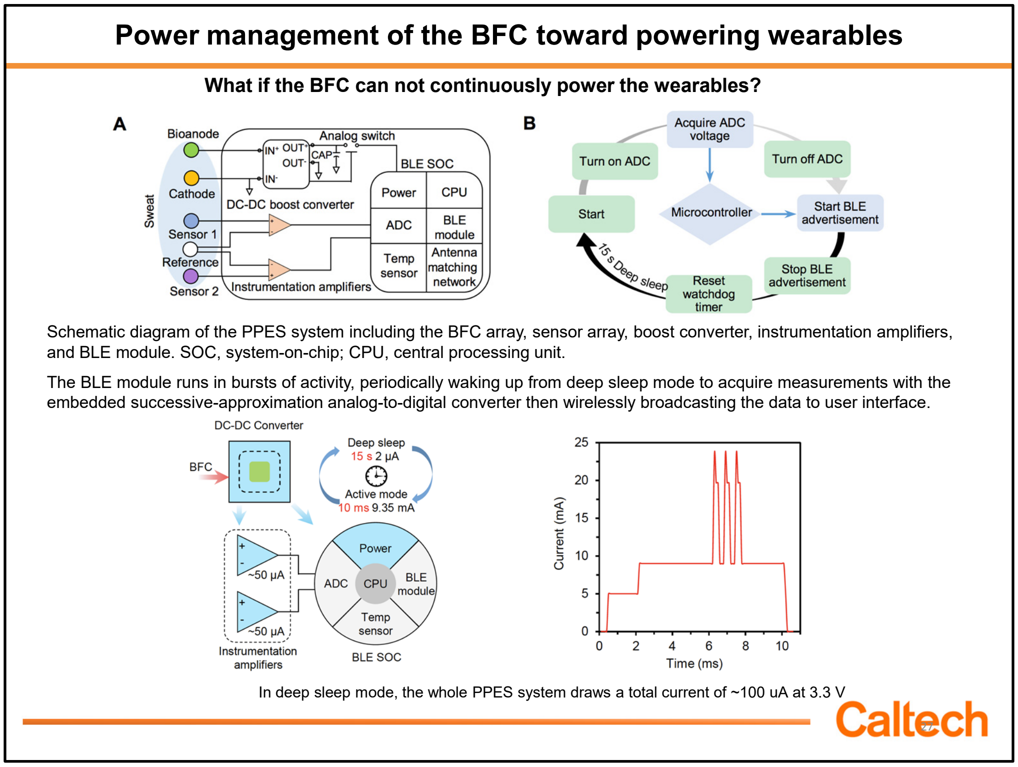


>> Wei Gao: We found that compared to platinum, platinum cobalt has much better performance because the transition-metal cobalt dopants could enhance the cohesive energy and stabilize the nanoparticles. In this case, the nanoparticles maintain their size even before and after you use them. We checked our device over time, and it had much better performance. If you use platinum, you see the voltage decreases very quickly. If you use platinum cobalt, you maintain similar voltage over time, for a pretty long time, in sweat.

Later on, we found that if we coat this platinum cobalt surface with a Nafion layer, which is a permselective layer, this can prevent or minimize the fouling. The biofouling effect is because when you apply voltage, the charged molecules can absorb on your electrode and block your sensing area and it can make your sensor performance actually go down over time. With this Nafion film, we get nearly the same performance, even if you use it continuously for over one hour. If you only use platinum, the performance quickly decreases. But using Nafion-coated platinum cobalt, you get identical performance over time.

We tested the stability vigorously: we tested our device in sweat continuously for 15 hours, and as you see, the voltage essentially remained the same. We stored the same biofuel cell over 24 hours and then tested it again for another 15 hours in sweat. We still got the same performance. That means the stability of the biofuel cell is extremely good in this case. It’s all because of the nanomaterial and nanotechnology innovation.

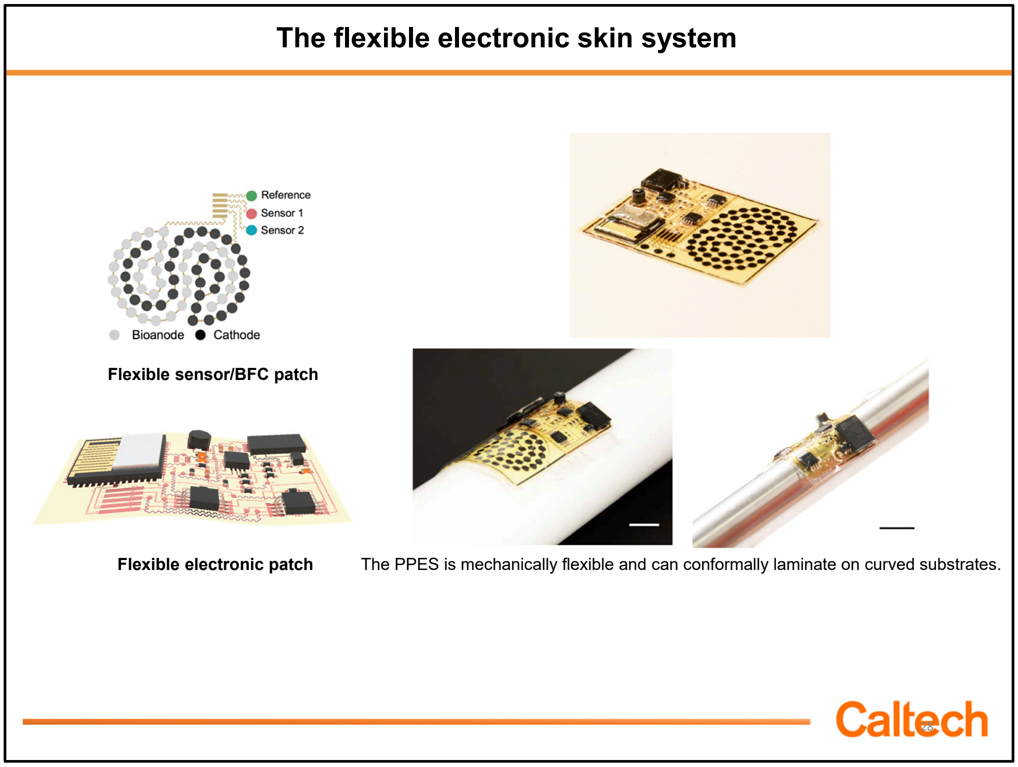
We already have very highly efficient biofuel cells. Now we need to think about how can we use this biofuel to power the wearables?



>> Wei Gao: Basically, we designed the system this way. The output of the biofuel cell goes through a DC-DC booster converter. Based on this, from this DC current to this current, the biofuel cell's operation voltage is low—it's 0.4, 0.5 V. But to power electronics, you need 2.2, 2.3, this type of voltage. You need to amplify the voltage, in this case, through the DC-DC booster converter. Then we can use this high-voltage electricity to power our instrumentation amplifier and power Bluetooth, power the microcontroller.

What if in this application, conversion, the power, is not enough? As I mentioned earlier, if you look at the power breakdown, Bluetooth consumes very high power. Real Bluetooth communication consumes 9-10 milliamps—very high power. It's very difficult for biofuel cells to continue to power Bluetooth.

We designed it this way. We let our Bluetooth sleep. We let the Bluetooth module sleep over time. Every 2 seconds we wake up the Bluetooth module. During sleep, the whole Bluetooth module—(including both) microcontroller and Bluetooth—consumes only 2 microamps—very low power. And while we activate it for 10 ms, it consumes 9 mA. Basically, we can use biofuel cell power to charge a capacitor, and when this capacitor charges to high voltage, we wake up the Bluetooth for 10 ms for communication, then put the system back to sleep for another ~15 seconds. For the overall system, if we use two sensors, the majority of the power comes from the instrumentation amplifiers—only 100 µA—and the total is only 102 µA, the whole system. When the Bluetooth is working, it consumes 9 mA (for 10 ms). With this sleep-wakeup-sleep-wakeup mechanism, we can achieve continuous sensing and communication. Every 15 seconds, we could send a packet, send data, to the user interface, to the cell phone. And we could do much lower periods, also, depending on the power we get from the biofuel cell.

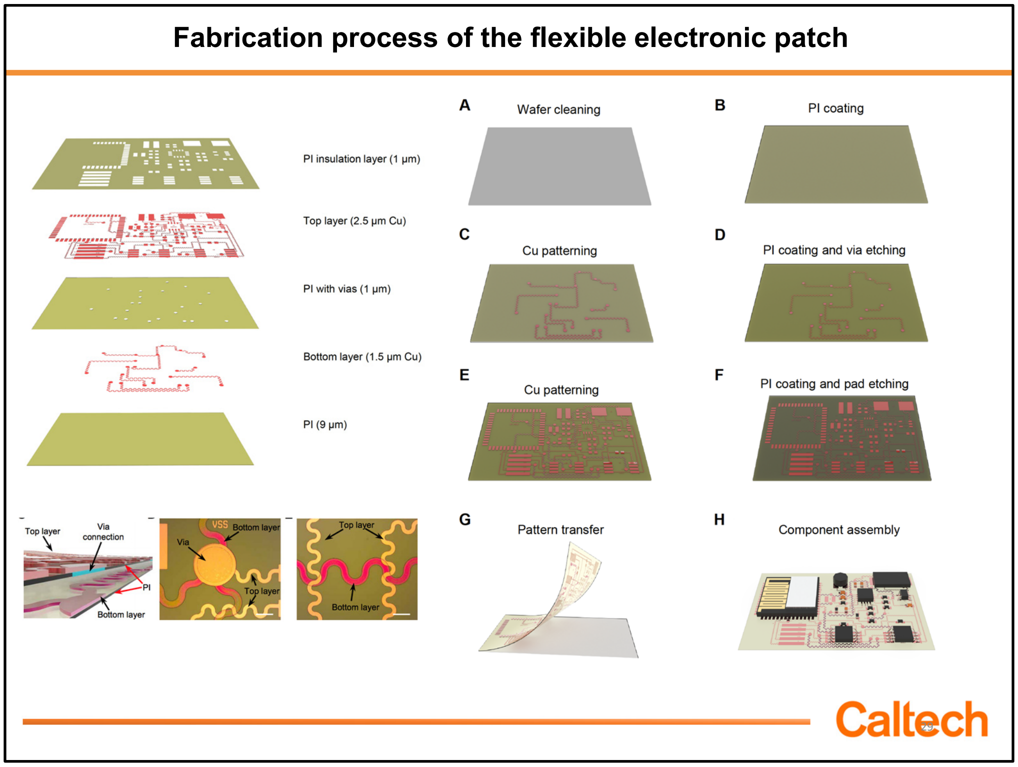


>> Wei Gao: We know how to continuously power the wearable. Now it’s time to fabricate and design our system. We designed a flexible system, as you can see here.

In 40 packages of biofuel cell systems, we call it the PPES (perspiration powered electronic skin). It is flexible. We can put it on a curved substrate, we can put it on our skin also, and we can bend it. So why do we need it flexible? Because our skin is undergoing different kinds of deformation while we are doing vigorous kinds of exercise. We want the sensor to be flexible so it can laminate on the skin and so it can tolerate different kinds of strain.

In this case, our sensor can have very good performance even in vigorous exercise. The sensor has two patches, two different parts, as you can see. This part, basically, is the flexible sensor and biofuel cell patch—electrochemical patch. This patch is the flexible electronic patch—the lower part. Put together, it's one system.

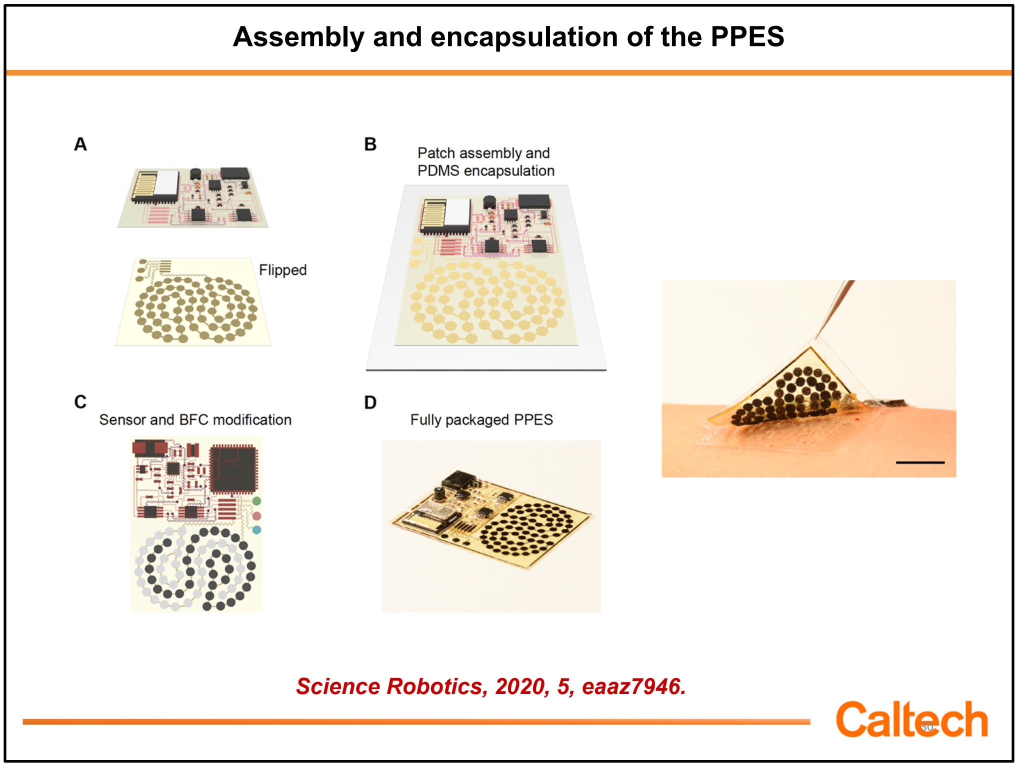
How can we prepare this? You see the sensors, it goes through the electronics, and the biofuel cell is also used to power the electronics. So how we can fabricate the patch?



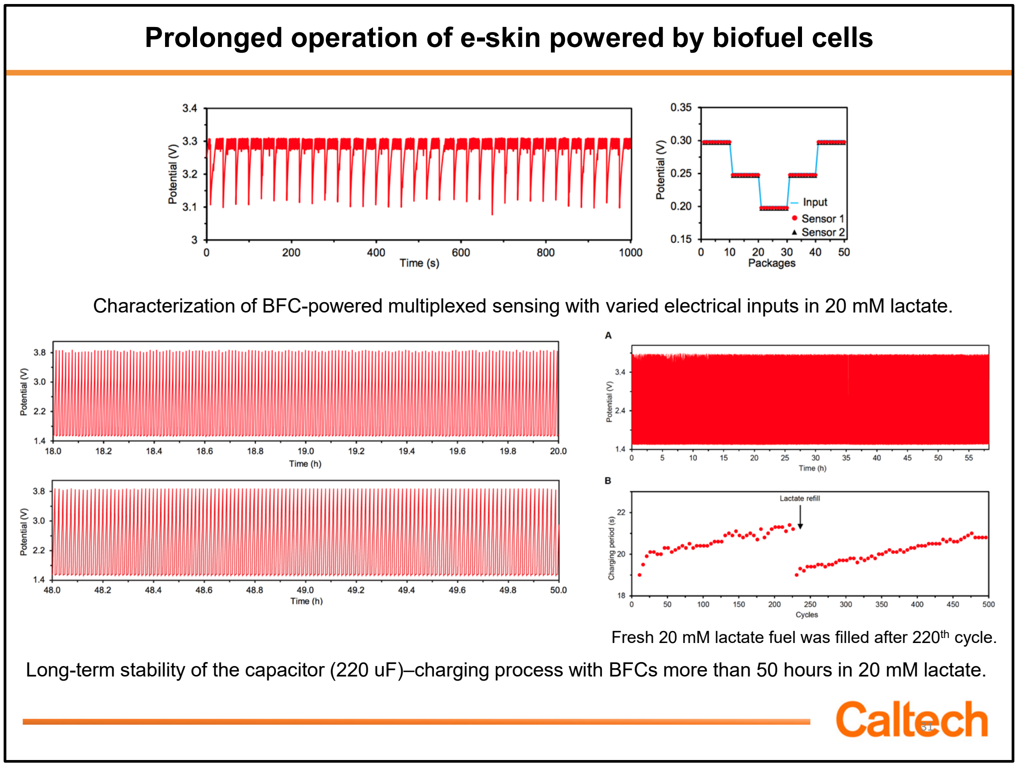
>> Wei Gao: The sensor patch, of course, is pretty easy. We can use metal evaporation followed by encapsulation to fabricate these metal electrodes. We can immobilize different kinds of sensors and biofuel cell anode-cathode on top of these electrodes.

For the electronic part, we use thin-film evaporation to pattern copper (copper is our conducting material). To make the multilayer design**,** we use a very thin polyimide (PI), a 9 µm polyimide substrate. Actually, we also designed these vias, the PI with vias, to allow us to pattern multilayer electronics to make the system more compact.

As you can see, the system after the pattern transfer is pretty flexible.



>> Wei Gao: Eventually, when we have the sensor patch and the electronic patch, we can assemble them together and we encapsulate the whole system with PDMS (polydimethylsiloxane) to make the electronic part, especially, fully waterproof. Thus, we don't have to worry about how humidity and sweat will influence the performance of the electronics. Basically, the whole system is waterproof.

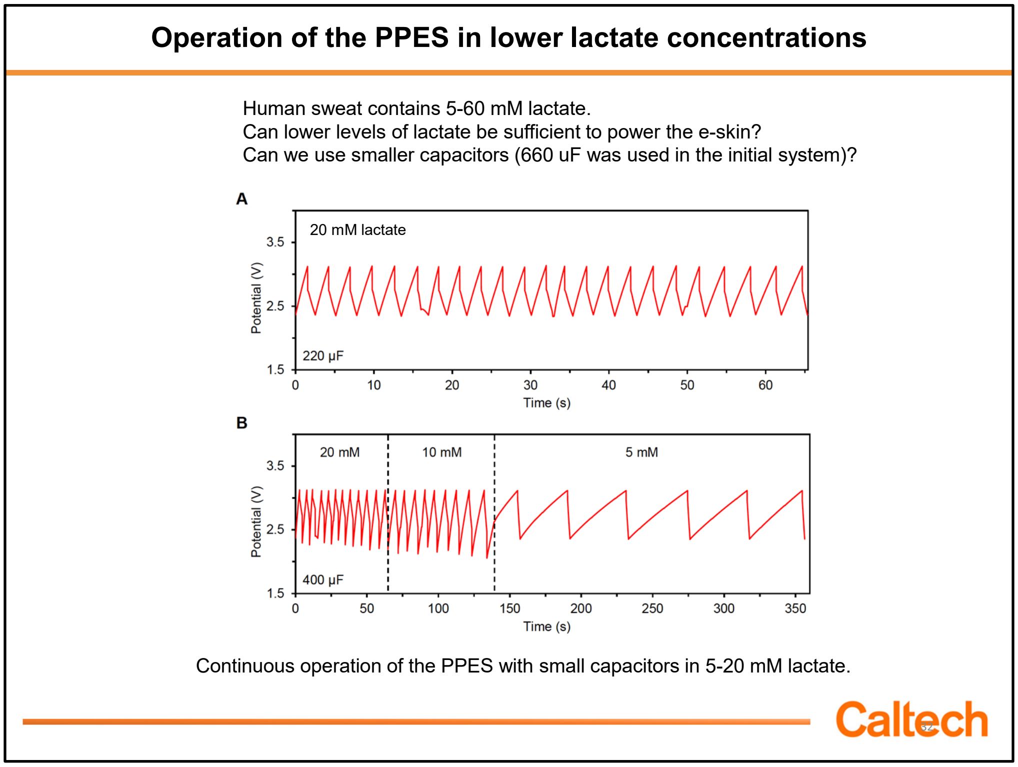


>> Wei Gao: After we have the whole system, we would like to check if the system can be continuously powered by biofuel cells. As you can see, by using 20 mM lactate, we can continuously charge our system, sense, and send packets. Whenever we send a packet, the potential will drop; we let the voltages stay between 3.1 and 3.3; send the package at 3.3 and discharge it at 3.1, and then charge it again. We send the packet back and forth, one cycle by one cycle.

If we give electronic input, voltage input, and measure output by the biofuel cell, basically, we can get the same response. It means this device can be used to measure the voltage output from the sensors.

In the case of long-term stability, we checked the system in the lactate solution for over 50 hours continuously. You can see, charging-discharging-charging-discharging, the whole system works pretty good over time.

The charging cycle slightly increases. Initially we thought, is it because the stability of the sensors turns worse? Later on we realized it's because of lactate consumption. If we put in the same solution over 50 hours , the lactate will be consumed, right? If you refuel lactate, the sensor performance comes back from the beginning. It means the system has super high stability.



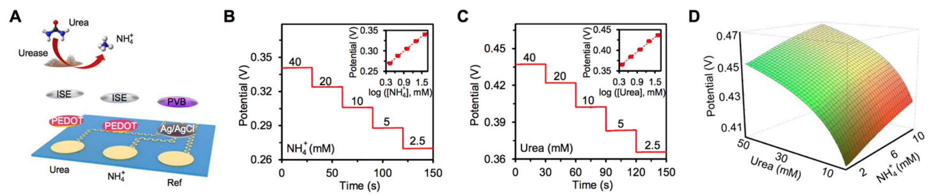
>> Wei Gao: We can use different kinds of capacitors. As I mentioned, biofuel cells use the charging capacitor to power the whole system. We could use 220 µF, 400 µF… the size of the capacitor will decide how long you will send the packets. If you use a smaller capacitor, of course you can charge it much faster.

By using 220 µF, basically every one to two seconds you can send the data. Even previously, when we did our continuous battery-powered system, we didn't need to send data every second; we just needed to send data every 3 or 4 seconds. Right now, for this biofuel cell, every second you can get data. It’s pretty impressive in this case.

We also tried to evaluate, can we use a lower lactate concentration, because different people have different lactate levels. It could be low as 5 mM or as high as 60 mM. The higher one, of course, no problem. What if the concentration is pretty low? We found that we can still charge the whole system; it’s just that the period for sending a packet is getting longer. It can take 10 to 20 seconds to send one packet, but the system is still working, even if you have the lowest lactate concentration.

PPES – Multiplexed Metabolic and Nutritional Monitoring

Urea and Ammonium Sensor Array



Characterization of the PPES for multiplexed biosensing

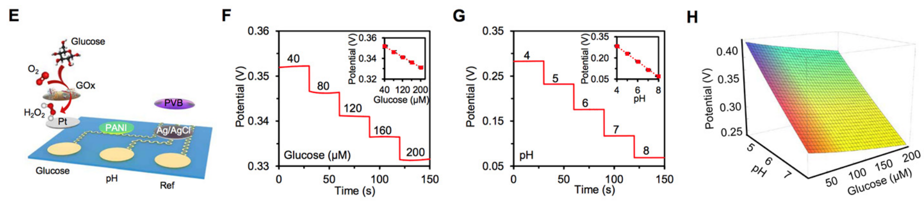
>> Wei Gao: So, we already have a very nice working system. Now we need to think about sensors. Initially we talked about our work to use our graphene-based biosensors to monitor some nutrients, metabolites, and stress hormones for different kinds of applications.

Here we try to address some new challenges. Can we design some new sensors, including for ammonia and urea? Ammonia and urea are very important conditions very closely related to our protein metabolism; they are also related to our kidney's health condition. The ammonia sensor is pretty straight forward; if we design an ammonia sensor, basically we just need to design an ion-selective sensor to detect ammonia ions.

But for urea, if you use the urea enzyme, it will generate ammonia ions. This means if you use this enzyme to develop a urea sensor, your result will be influenced by the ammonia levels in your sweat. In this case, to design the ammonia and urea sensor array, we will use the ammonia sensor reading in real time to calibrate the urea sensor reading. By using real-time calibration from the system, you can get accurate readings for both ammonia and urea.

Biofuel-Powered Soft Electronic Skin for Multiplexed Wearable Sensing

Glucose and pH sensor array

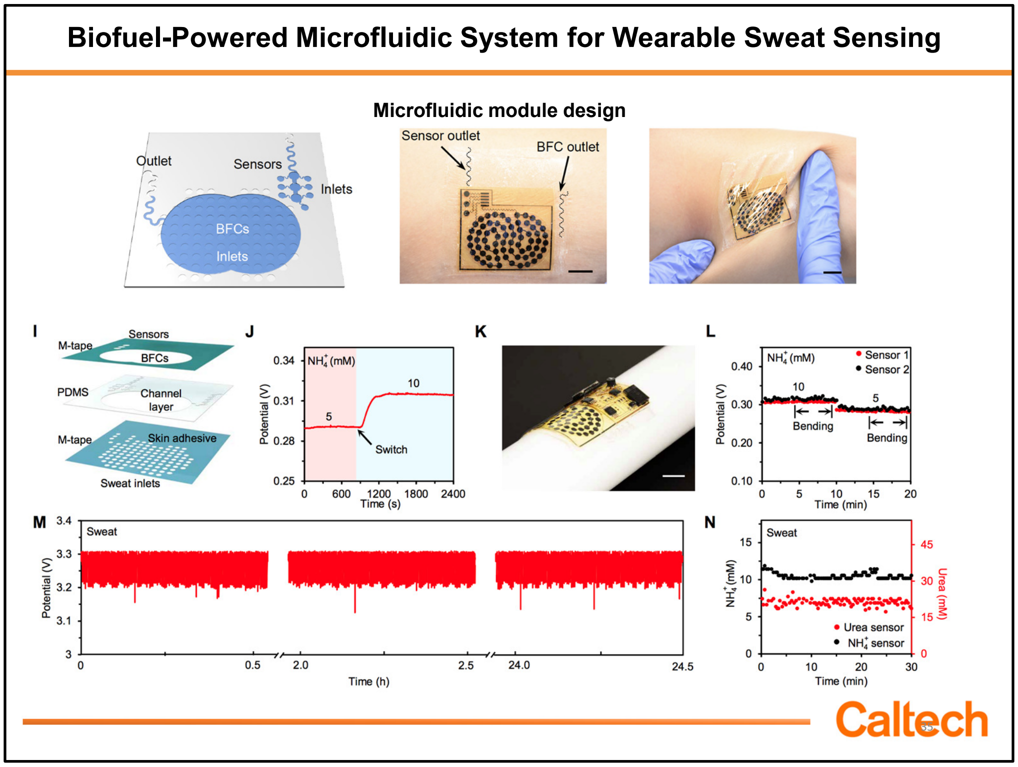


Characterization of the PPES for multiplexed biosensing

Caltech

>> Wei Gao: A very similar case for glucose. Non-invasive glucose monitoring is super important. Can we monitor glucose from sweat?

We developed this glucose sensor, but the glucose sensor has some considerations as well. Basically, sweat pH, there is a lot (of variation). It's different from our blood pH or saliva pH, which has a small variation. Sweat pH can vary from pH4 to pH8. That means it could have a huge error if you monitor glucose continuously without recalibration. So we could use glucose in the pH sensor array to do real-time pH measurement and glucose sensor calibration to get accurate information for glucose (levels).

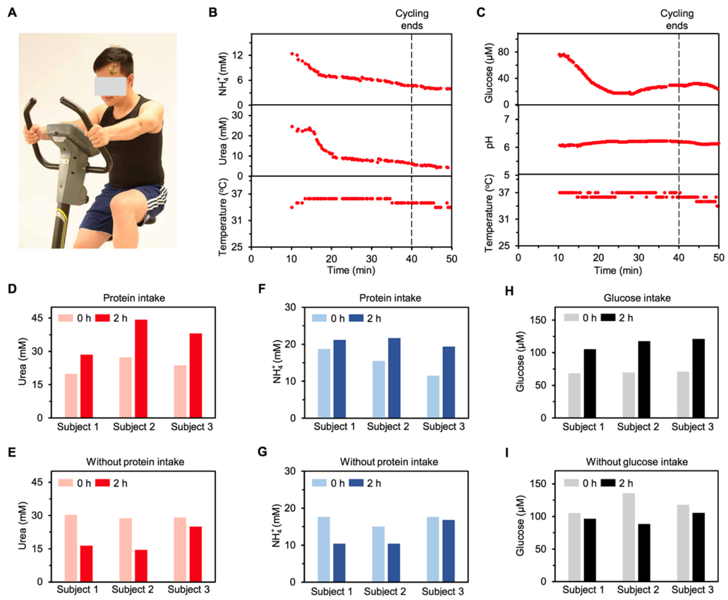


>> **Wei Gao:** When we put all the systems together, how can we sample sweat and analyze sweat from the skin, right? So what we designed is a microfluidic channel, by laser cutting as well. This microfluidic system, as you can see, is pretty salty from the skin. When sweat comes out, it will enter the microchannel, power the biofuel cell, and power the sensors.

Using microfluidics, you can minimize skin contamination influence and minimize the influence from the sweat evaporation as well. You can still get a very high temporal resolution for biosensing.

So eventually, we use sweat, real sweat, to power the whole system, as you can see, continuously, for many hours. We get a very stable performance of the system. It means that we are basically using this device for wearables studies—on-body trials.

Biofuel-Powered Soft Electronic Skin for Wearable Sensing

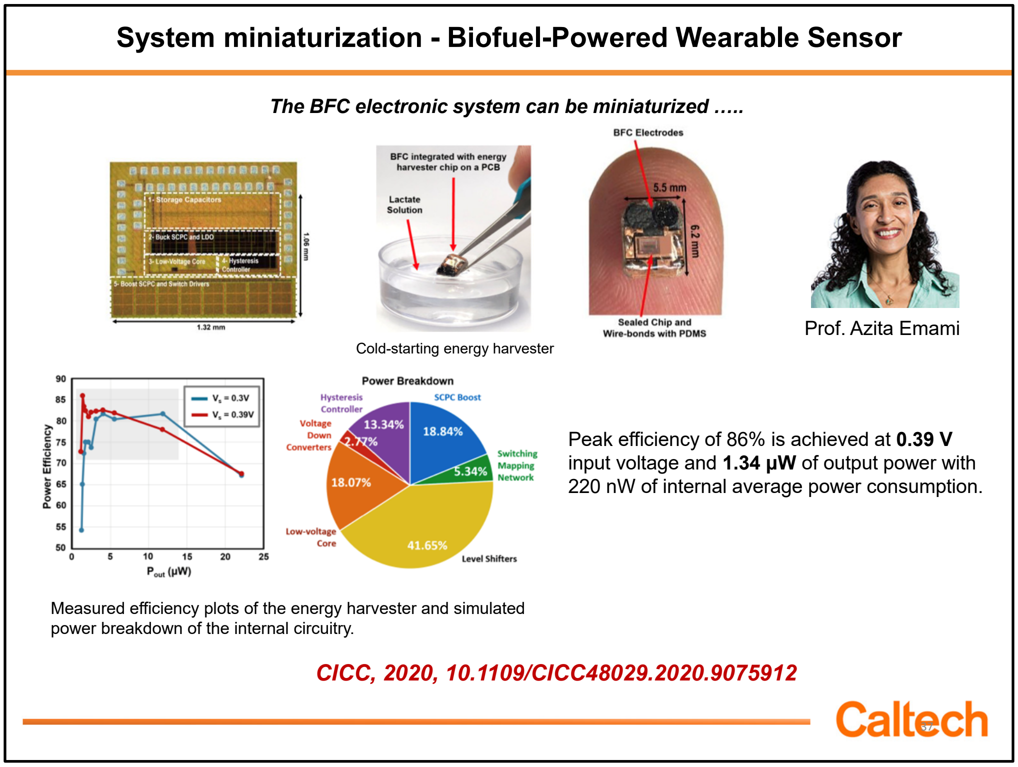


On-body evaluation of the PPES toward personalized metabolic monitoring.

>> Wei Gao: Here is the device, worn by a subject. We can real-time check urea, ammonia, glucose, pH, over time while the subject is doing physical activity.

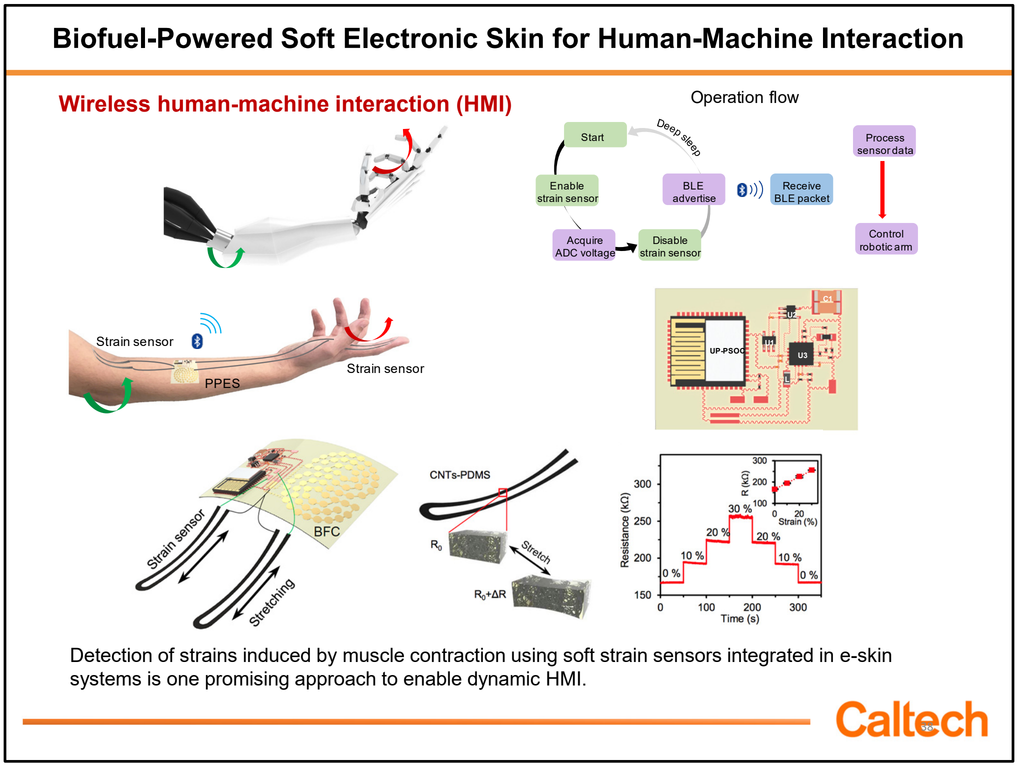
We can also check, basically, the nutrition you are taking. When you take protein, when you take glucose, you can use our device to continuously track your metabolites and nutrient levels in your body. That's the purpose of continuous monitoring. We want consumer data from people, and we can get a unified set of data to give guidance to the subjects how to control their diets, how to minimize the risk to developing metabolic problems.

So of course, this biofuel-powered platform can be expanded to our other wearable sweat sensing applications. Here we only show the four sensors. Of course, this device can be used to monitor other targets. We could use this self-powered, biofuel-cell-powered wearable system for other wearable applications.



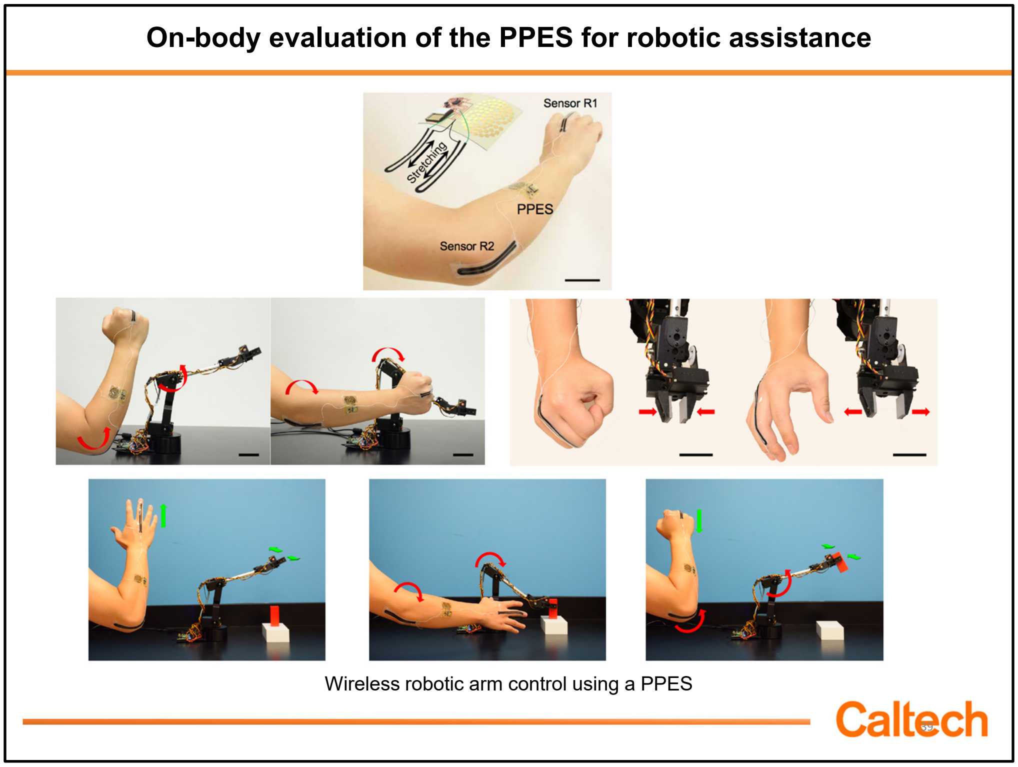
>> Wei Gao: We can make this system smaller. We can also miniaturize the power of the system. Working together with the electrical engineer, Prof. Azita Emami of Caltech, the Electroengineering Chair, we designed this integrated circuit. This chip, as you can see, is only like 1.3 x 1 mm, super small. With this small chip, the power consumption is very small, as well; you can see, output power is 1.3 µW. And in this case, within a very-small-area biofuel cell, we can power the biosensors already.

So this is a highly promising approach. As you can imagine, you could integrate many sensors here, still using a very small biofuel cell that can power multiplex sensing. It's very promising for wearable applications, especially, toward commercialization, if we can make the sensor smaller, lower-power, and it can be easily integrated into other wearable platforms such as a wristband.



>> Wei Gao: In the last two slides I want to share with you other applications, other wearables, how we use our biofuel cell to power electronic skin for human-machine interaction.

Right now, there are people already working on using these sensors—strain sensors or physical sensors—to control a robotic arm. We could actually perform gesture recognition basically through monitoring the muscle contraction using our soft strain sensor; we designed this carbon nanotube-PDMS elastomer-based strain sensor; we can integrate it on to this wearable platform; we could use our biofuel-cell power in the skin to detect the strain from our hand and from our wrist, and we can use this device to control remotely, wirelessly, a robotic arm, for example.



>> Wei Gao: Here, as you can see, it's a battery-free system. You can control the moving of this robotic arm, you can also control opening and closing of this robotic hand for capturing a target.

So this is just a proof-of-concept demonstration. We could use this tool in more advanced robotic platforms.

On-body evaluation of the PPES for robotic assistance

The use of the PPES for robotic prosthesis control

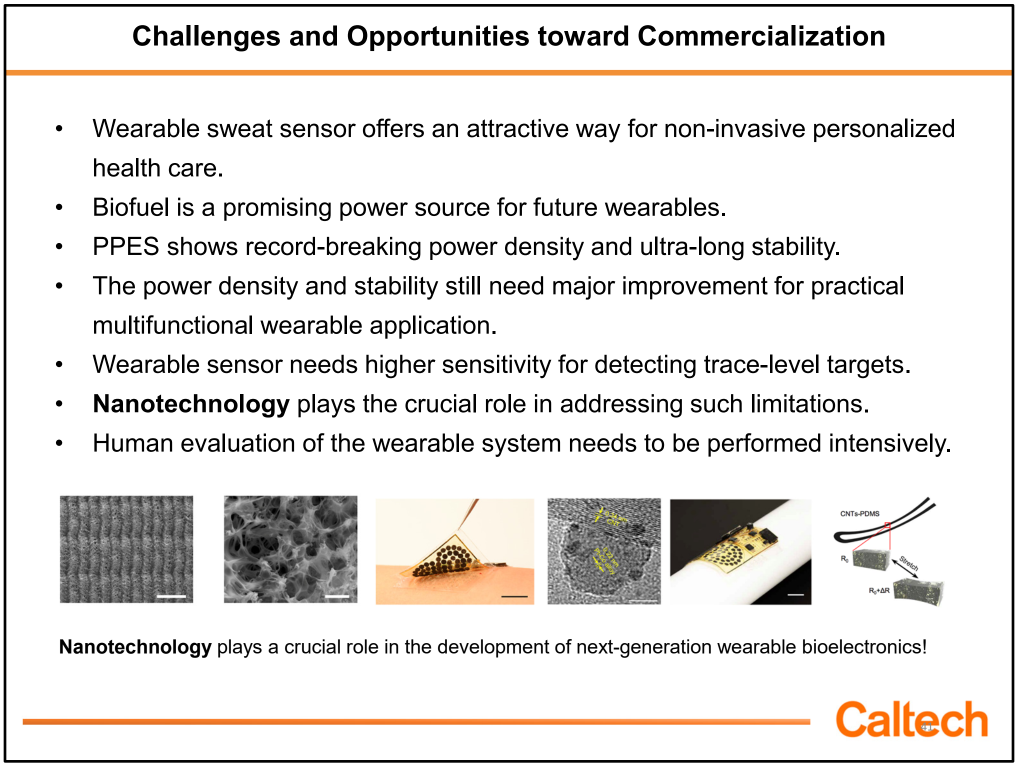
The multimodal PPES could facilitate the design and optimization of novel prostheses that bring the human into the loop of prosthesis control to enable real-time user-specific responses to human intent and behavior

Science Robotics, 2020, 5, eaaz7946.

Caltech

>> Wei Gao: For example, this is a prosthetic leg. We could use our sensor to control a robotic leg. Because this robotic leg is for people who need assistance, they need to use their own information, their own gestures, to control what they lack. In this case, we could use a prior device to monitor strain, again, to control the robotics and movement for robotic assistance.

I would say this is a simple proof-of-concept demonstration, but the potential is much more here. We could potentially use our biofuel-cell-powered system to monitor both strain (physical information) and chemical information, especially when we incorporate other vital signs such as EMG (electromyography) and EEG (electroencephalogram) signals, along with metabolic biomarkers: we could use this personal information to optimize this prosthetic control and prosthetic design for future generations of medical robots.

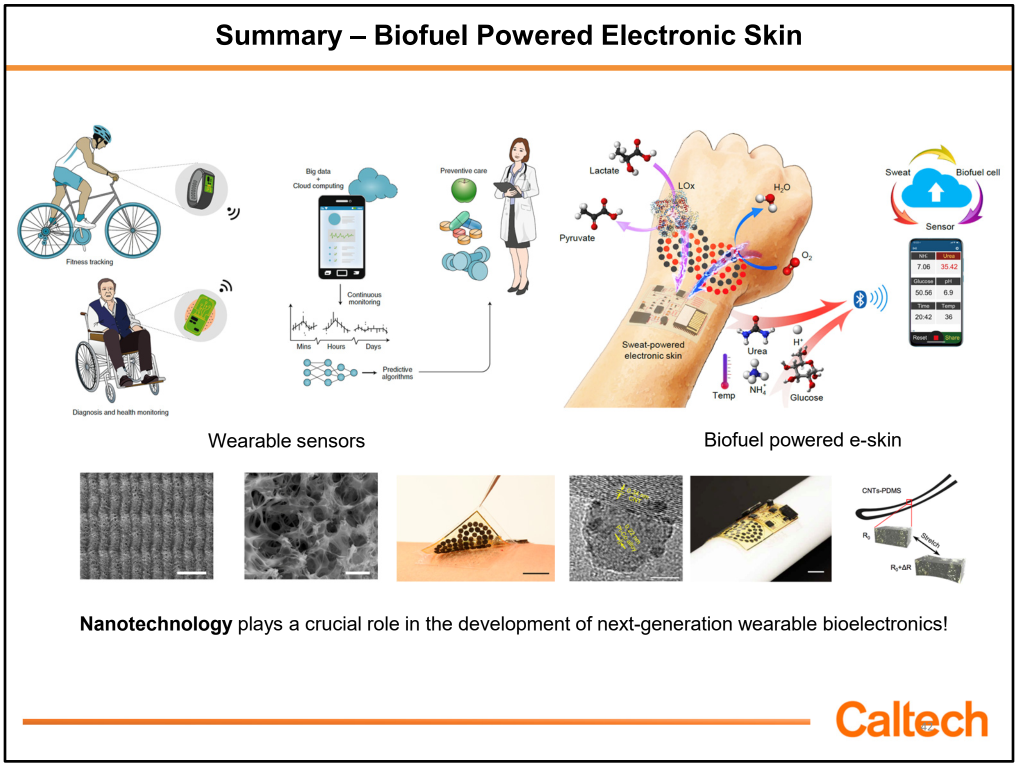


>> Wei Gao: To summarize, we already developed this biofuel cell platform and we showed the potential of this platform basically for wearable sweat sensing for different kinds of personalized healthcare applications.

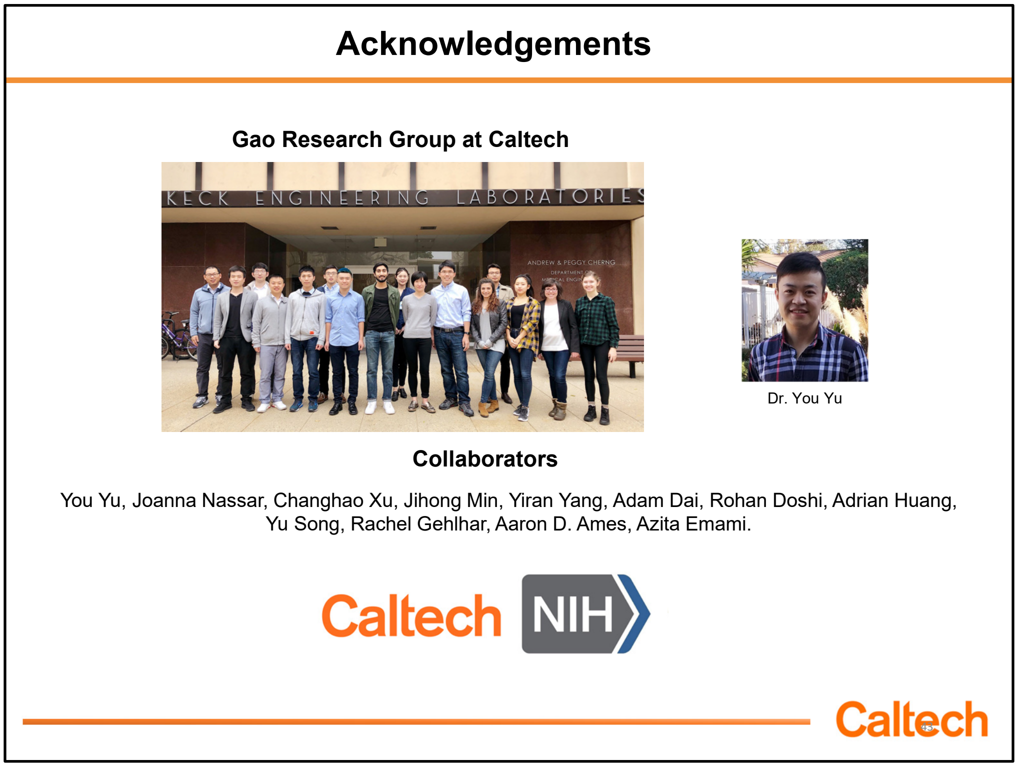
Biofuel cells, such as sweat lactate, could be a promising source to power future wearables. And through nanomaterial innovation, we designed highly sensitive sensors and high-performance biofuel cells with real calibrating power sensing and ultralong stability.

Of course, before commercialization, we still need to further improve the density and stability to allow the device to be used for a superlong time and to power different kinds of advanced functions from this wearable wristband, for example.

Overall, I think, this field requires further technology innovation—from materials, from devices, and from systems—and we will need more human evaluation to find more and more killer applications.



>> Wei Gao: I believe this type of wearable sensor could play a very important role in future personalized healthcare, as I mentioned earlier. We can continuously collect data to track our fitness condition, for disease diagnosis, and very importantly, the large set of data from the wearables could be used for numerous fundamental, clinical, and preventative applications.



>> Wei Gao: I would like to thank my research group at Caltech--this is my team--and particularly Dr. You Yu, who is the lead author for this biofuel cell paper. And I also want to acknowledge our funding support from Caltech and from NIH.

Thank you very much for your attention.

Thank you for your attention!

Questions?

For more information, please visit: http://www.gao.caltech.edu/

>> Wei Gao: I would love to answer any questions you might have.
For more information, please visit the Gao Research Group at Caltech.

Q/A

How do you keep the sweat from clogging and drying out in the microchannel?

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>> Stacey Standridge: Thank you for a fascinating presentation. We've seen quite a few questions come in during your presentation, and we'll try to get through as many of those as we can in our last couple of minutes. If anybody else who is listening still has questions, feel free to submit those in the Q&A box, and we'll try to get to those as well.

We'll start off with a question that came in towards the end of the presentation; they wanted to know, how do you keep the sweat from clogging and drying out in the microchannel?

>> Wei Gao: Basically, as I said, we designed this microchannel to minimize the influence from skin contamination and sweat evaporation. The microchannel has an inlet from the skin. Once sweat comes out from a sweat gland, it will enter the microfluidics, and it will go outside after passing the sensor through the outlet**.** Basically, sweat will flow out and it will not stay inside.

Of course, there will be sweat inside eventually. Eventually, while we use it, even if a little bit dries out, when new sweat comes, it will refresh the whole system. So this device can be used for a very long time, continuously. We have an outlet, basically.

Q/A

What types of substrates are best suited for wearable sensor applications, and specifically, is carbon cloth a suitable as a substrate after modification?

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>> Stacey Standridge: Wonderful. The next question was on substrates. Someone asked, what types of substrates are best suited for wearable sensor applications, and they specifically wanted to know, is carbon cloth a suitable as a substrate after modification?

>> Wei Gao: That‘s a very good question. We certainly want to design the sensor for better wearability, and right now for our microfluidics and this soft skin patch, we are using medical tape to put the patch on the skin. A medical tape is more flexible and it's more biocompatible, and thus is more suitable for wearable sensor application, I think.

I would say, when you say which type of substrate, of course it's medical-grade adhesive. Our sensor is disposable: you can peel it off and throw it away eventually. For the carbon cloth, it's a promising substrate, of course. I think for direct contact with the skin, I do suggest some medical-grade adhesive.

Q/A

What are the volumes and collection times needed for the cortisol concentration determination in sweat? Would you be able to classify a person's emotions using the sensor, and when you monitor the stress level, how quickly do you get results — do you need a full day or 2 seconds?

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>> Stacey Standridge: Thank you. A couple of questions came in specifically on the cortisol sensor you spoke about at the beginning of your presentation. One was, what are the volumes and collection times needed for the cortisol concentration determination in sweat?

>> Wei Gao: Basically, it depends on how fast people sweat. We only need a few microliters of cortisol, a few microliters of sweat, to analyze the cortisol level. That means, a few minutes is sufficient for us to monitor to get enough sweat to analyze cortisol, at the levels of 2-3 minutes I think.

>> Stacey Standridge: Another question on the cortisol sensor was, would you be able to classify a person's emotions using the sensor, and when you monitor stress levels, how quickly do you get results (a bit different from collection times)—in a full day or 2 seconds?

>> Wei Gao: We want it to be as short as possible. We found that for our sweat cortisol sensor, we can get it within one minute. Commercially, I would say the gold standard ELISA will take a few hours. But for a stress response, you want it as short as possible, because we care about the cortisol level—it fluctuates very quickly in the body. We want to make the analyzing time as short as possible; that's why right now, overall, we use a few minutes.

The question of the person's emotions is also a very good question. We are trying different kinds of stressors right now. In our published paper we showed two stressors. One was vigorous exercise, the other was the cold pressor test, a standard pain test. Right now, we're also incorporating a type of emotion analysis as a stressor to create different kinds of mental stress, that analyzes the cortisol change. We will be able to capture the cortisol change when we apply this emotion stressor to a subject. We are working on our IRB (Institutional Review Board), and we are extending our study toward different kinds of stressors.

Q/A

Does the sweat composition vary on the location of the body and where you place the sensor?

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>> Stacey Standridge: Thanks. We have a lot of questions coming in. Thank you to everybody who is submitting them. A couple of questions, actually, on does the sweat composition vary on the location of the body and where you place the sensor?

>> Wei Gao: That is also a great question. I want to say, it depends. So, in general, the sweat does vary from part to part. Sweat secretion is a complicated process. It can be influenced by the types of sweat glands and basically the sweat rate. Some biomarkers, their levels depend on the sweat rate; sodium and chloride, they are actually related to the sweat rate.

But some markers are independent to sweat rate, so when we reanalyze the target, sweat rate is a very important consideration; this is actually related to the location, of course. So, we do develop some sweat rate sensors that could potentially allow us to do better calibration. But the way I show, for example, uric acid and cortisol, we did not consider sweat rate. We still got very high correlation factors for both, around 0.85-0.9, already. I could imagine that incorporating this calibration of sweat rate, we could potentially get higher correlation factors.

Q/A

Have you worked with 3D printing for sensor fabrication, and if not, do you think this is a feasible option?

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>> Stacey Standridge: Thank you. Here is one that is a little bit different in theme from some of the other ones that have come in. Someone was wondering if you have worked with 3D printing for sensor fabrication, and if not, do you think this is a feasible option?

>> Wei Gao: Yes. I think 3D printing is a very promising approach. We do have a 3D printer in our lab and we are trying to view the prototype for the device. Right now, we have not tried 3D printing for sensor fabrication. We mainly use 3D printing for prototype development; for example, if we develop a watch, how we can make the cast, right? But I believe we are actually—our lab is actually—purchasing a nice 3D printer. We are thinking, at least I believe, 3D printing can be suitable for sensor fabrication.

>> Stacey Standridge: Thanks. And I think our last question of the webinar will be, since your biofuel cell works on input from sweat, do you think it can be modified to be an implantable cell, for a heart sleeve, perhaps, by charging the cell using something other than sweat?

>> Wei Gao: Yes, of course. We design our lactate biofuel cell from the skin because, as I mentioned earlier, our sweat contains very high lactate levels—5-6 mM—and it's a promising way to power skin devices, for our sweat sensors. This biofuel cell technology could be applied for implantable devices to power the implant. Actually, people are already working on that. In this case, most likely we will need a glucose biofuel cell—a very similar concept to our lactate biofuel cell: just replace the enzyme lactate oxidase with glucose oxidase. We could implant this device inside the body for continuously charging or powering internal medical devices. I think some people already demonstrated proof-of-concept using glucose biofuel cells for powering some simple implants.

Closing

Final remarks

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>> Stacey Standridge: Thank you. Thank you, Dr. Gao, for a truly interesting presentation today, and thank you to all of our audience for tuning in today and submitting so many wonderful questions. I'm sorry we couldn't get to them all in the time that we had. With that, I just want to thank everybody for their time.

Please feel free to continue to check nano.gov for updates on the National Nanotechnology Initiative. We will post the archive of this webinar there as well. Thanks!

>> Wei Gao: Thank you.