**Introduction + Purpose + Keynote**

00:00 → 11:21

**Ralph Etienne-Cummings:** All right. I think it's about that time. Thank you so much for showing up for coming to the neuromorphic principles in biomedical, biomedicine, and healthcare. So my name is Ralph Etienne-Cummings. I'm one of the Organizing Committee members and these are us. If you will, who have attempted to patrol and twist arms and get you over here for this meeting. So we have Dr Jennifer Blaine Christen from Arizona State, Dr. Duygu Kuzum from UCSD, Luke Osborn from Case Western. I can call him Luke, he was a student in my lab, so I can refer to him directly. Dr Valero-Cuevas from USC and then from the NIH, we have Grace Hwang, who has been one of the drivers of this of this meeting. Thank you, Grace, for all the hard work that you put behind it, as well as Jessica Falcone and David Rampulla. So together. At least that's the organizing folks that tried to put together this workshop with the help of folks that were on the technical committee Shantanu, Gina, Gert, Sydney, Robert, and Sunny will be collecting ideas and synthesizing them and trying to generate a more cohesive discussion points for the afternoon, where we will then try to put together a roadmap hopefully going forward for the community. So this is us trying to put things together. The goal of the workshop. I thought it would be useful to give a little bit of a snapshot of what we are trying to do here. So the idea is to bring together folks who work in biomedical and neuroengineering technologies and to think about some of the benefits of neuromorphics from the perspective of power and data efficiency, adaptability performance, and see how these techniques that are common to if you will to the community of neuromorphics. How can they benefit biomedicine and healthcare? We think that ultimately it's a question of leveraging ideas that we see and learn from biology and then translating that into a problem. Solve problems, solving processes that can be useful for biomedicine and healthcare in the end. At the end of the workshop we hope to put together a a roadmap that all of you, I hope, will contribute to that will provide a kind of a plan of where we go forward from here, and how the various funding agencies can help us move. You know the various pieces together. So thank you again for coming to help with this. So two days are organized as follows, the 1st is starting from the cortical side of things, thinking about what are the neuromodulation steps that happen in dealing with diseases and disorders that happen in the cortex, and the various ways by which you know, clinicians think about this right? So most of the time I found that whenever we are dealing with engineered solutions, unless you understand what the clinicians need it is hard to develop technologies that will help the clinicians right? So getting a view from the clinicians. Perspective is important, and that's what we spend the 1st session working on. Additionally, then from there, we move a little bit to the periphery. A little bit of linking with technologies when we go towards prosthetics. So Luke and Francisco will be leading the second session that deals with this aspect of it before we get into the afternoon where there'll be some poster presentations as well as a moderated discussion. Please come with your arguments with your discussion points and your hats on. We want to have a vibrant atmosphere, robust discussion to the point where, you know, after we synthesize it all, we can come up with, you know, with a plan that makes sense. Going to the second day, we start with devices. So what are the technologies that will ultimately end up facilitating the two pieces that we've heard about on the 1st day? To the point where we move to the 4th session, which will be more about applications and thinking about a more global sense of how do you come up with a systemic theory that describes it all and tries to blend it all together. So that's the flow of what we'll be talking about today and tomorrow. So just to give a little bit of a background of what neuromorphic means and why we are thinking about neuromorphic. So we know that nature basically inspires machines. Right? So there are two ways that that one can think about that you can think about from a form perspective. Additionally, you know the classic example is how Antoni Gaudi used it. The Nautilus shell to develop the framework for Casa Mila. You guys have been to Barcelona. I'm sure I've seen it, and that's an example of a direct kind of form to engineering solutions, right? But there's also the other part which is more like function right, when you think about how Leonardo da Vinci was influenced by seeing a sycamore plant fruit falling, and that turn and that flow gave the idea of hey maybe a helicopter can be drawn from that perspective. Right? So over the years, that same kind of concept has been applied to the nervous system. So you think about the latest Nobel Prize that was awarded in physics to John Hopfield and Geoffrey Hinton with John Hopfield, who thought about the architecture of associative memories by constructing networks of resistance and memory elements, threshold elements in order to create a self-associative memory. But even before that, you had the work of Paul Mueller and Carver Mead, where they basically tried to understand the fundamental actions that were going on at the cell membrane and trying to compute, translate that into transistors, and integrate that into neurons or models of neurons, and so on. Additionally, more recently, we've had systems of these networks being put together to create, like, for example, the Spinnaker network. We have folks here from Brainchip, who work on other types of networks as well that you'll be hearing about as we go along, and not to forget folks like Eric Vittoz and Misha Mahowald who have also contributed significantly in this kind of nature-inspiring electronics. Incidentally, there is a prize called the Misha Mahowald Prize that is awarded by the Institute of Neuroinformatics from Zurich that I suggest that you guys look out for as well. It's time for nominations. So please do take a look. Additionally, this is for both early career as well as late career, types and groups. So with these things in mind then. You know it. It's useful to think about how to model and how to think about the various degrees of granularity that we find in the nervous system. So this plot, this drawing, comes from Gert Cauwenberghs, who is one of our technical committee members who's unable to come in person. However, he's online. That basically shows the different layers by which folks are thinking about modeling the nervous system at the singular single channel levels, where you can basically think about a single transistor, the way transistors operate in subthreshold, being that type of an example all the way through to the entire or the to the top of the nervous system. which is the entire brain. How computation is done, for example, for attention, or how various other computation pieces are put together, and that interaction between the two,. Thinking about how you know what we've seen develop in the deep brain, deep networks or other types of work like, for example, Tomaso Poggio's work on HMax, when he was thinking about that. However, that's also an example of essentially layered networks that flow from this notion of looking at biology for inspiration and then developing computation ideas. Additionally, then there's the interaction between the two going top down, bottom up, and so on. So it's important to think about everything in that continuum of the nervous system that we're looking at here. Additionally, then this little slide here from one of the papers from my lab which tries to show where there are places where neuromorphics might be useful in diagnosis, places where it might be useful in neural interfaces as well as biological analysis and neuromorphic tools. So all these come together is the. I'm hoping that we'll come out of this these discussions that we'll have here, and come up with a roadmap of where we should be investing, moving forward. So with that in mind, let me just kind of close with this last slide. We've seen essentially an evolution of the term neuromorphic over the last few years. It started as being strictly a hardware-specific notion. How do you build particular circuits that mimic the nervous system? But over the years it has kind of flown from low-level, sensory processing all the way through to now thinking about algorithms for AI and data science in a general sense and acceleration for computation, and so on. Now we are thinking about something more useful if you will. Applications in the space of healthcare environments. Additionally, this is what I'm hoping that we will gain here and move things forward. So thank you so much. This is the end of the introduction. So our 1st couple of speakers, short speakers, are going to just basically be the important folks in NIH and NSF that have made this funding possible, and I shall start with Jessica telling us who's going to say.

11:22

**Jessica Falcone:** Next, I'd like to introduce Dr. Andrea Beckel-Mitchener. She is the Deputy Director of the BRAIN Initiative at the NIH. The floor is yours.

11:37 15:23

**Andrea Beckel-Mitchener:** Good morning, everyone. It's really nice to be here. I'm delighted to represent the NIH BRAIN initiative at this meeting. So on behalf of the BRAIN Initiative and our director, John Ngai, who could not be here. We want to welcome you both in person and our virtual attendees. I don't know how many there are, but I understand there's quite a few. so we're excited to be part of this workshop, and I'm looking forward to learning new things. As many of you know. The broader NIH BRAIN Initiative started about a decade ago with, it's a global effort. Additionally, it's the focus of discovery and technology development. All understanding the human brain better, its parts list, its architecture. So we started funding grants at the NIH in 2014. And at this point we've invested over 3.5 billion dollars in hundreds of projects in the last 10 years, and there have been just some remarkable discoveries that we're truly excited about. We really think many of these are going to be game changers in how we understand how the brain works. However, we don't want to rest on our laurels. What we're looking for now is what the next new areas are where we can start applying some of these discoveries. And we're very excited about neuromorphic engineering and systems based on neuromorphic principles. And I think that's why we're all here today. So I just want to make sure I hit all the high points here. So one of the directions that we do believe in is some of the technology that will arise from this, as we just had a nice introduction of the possibilities. There are many new architectures, new energy efficient computing devices, novel algorithms that will help us understand the brain. We're going to learn more about health and disease. There will be innovative device designs that come out of this. And I know we're focused on biomedical applications here. However, we might just save the planet along the way, so no pressure, no pressure at all. But we are looking forward to everything that we have to offer from this field. One of the things that we can do now, so many of you may know about the NIH BRAIN Initiative. We have a very assertive data sharing policy. So we're looking at wiring diagrams of the brain and multiple organisms. There's a lot of functional measures, electrophysiology, that is the data are all archived in our NIH supported archives as well as the parts list the cells that process or that act as the processing machines for these circuitry. We would love for the field to access those data and start using them in ways and understanding them in ways that will help this field move forward. So we really do encourage their use. They are pretty much open access for research purposes. Again, whether you're an engineer, neuroscientist, a computational biologist, a clinician, we need everybody in the room talking together. This is sort of part of the DNA of the BRAIN Initiative that we have recruited, not just biologists, the traditional grantees of the NIH, but the BRAIN Initiative really does have a large representation of people from the physical sciences and from engineering. And we found that that has been so fruitful in developing these new technologies and these new approaches. So we're really looking forward to more of that. And, as I said in my first sentence, I personally am looking forward to learning a lot in the next couple of days. So thanks very much, and look forward to it.

15:38 --> 16:40

**Grace Hwang:** Thank you, Andrea, for those wonderful inspirational remarks, now I'm Grace Hwang, and it is my pleasure to introduce Dr. Paul Lane. who is the acting Deputy Division Director of the ECCE, which stands for Electrical Communications and Cybersystems Division within the Directorate for engineering at the National Science Foundation. I am especially pleased to see Paul here. He holds a very special place in my memory when it comes to neuromorphic engineering. Back when I was at the NSF, I was a program director where I conceived of a program and he very much brought the materials perspective and the energy efficient perspectives to me. So it is great to see this multidisciplinary group. And I would actually say for the material scientists in the room that was a direct inspiration from Paul Lane.

16:45 --> 19:04

**Paul Lane:** Thank you, Grace. It was a great pleasure to work with Grace while she was at the NSF and I'm glad we had the opportunity to renew our acquaintance. So I'd like to start with a famous line from The Graduate. Although updating it slightly. Our protagonist, Benjamin, is at a party with a bunch of older individuals. One man comes up to him and talks about the future. He says one word: plastics. We're here to update that. I might say one word: energy. There are transformative advances in society we're seeing now in medicine from artificial intelligence, generative AI, large language models. They all require enormous amounts of energy. If you ever fly into Dulles Airport and go north of there, you'll see data center after data center after data center, each consuming megawatts of power. And so applying neuromorphic principles to new circuit designs, devices and materials from the bottom up will be essential. As a result, I am delighted to be here and welcome you on behalf of the National Science Foundation. When I first joined the NSF in 2018, I became interested in neuromorphic. I would say techniques in seeing individual programs across engineering, the Computer Science Directorate, not so much materials at the time, and moved to broader programs the Brain Inspired Dynamics for Engineering Energy-efficient (BRAID) computing initiative that Grace keynoted. If you look at our Future of Semiconductors program, you will see neuromorphic all throughout it in terms of spintronics, memristors, phase change materials, novel gating concepts, ion gating, even string gating. Now, and coming up for the future, there's going to be the addressing system challenges through engineering teams that was just announced. I presume the design materials were revolutionizing engineer our future, which is how we participate in Materials Genome Initiative, that the work being done in the field and by the individuals here is critically important to the advances that the National Science Foundation prioritizes and something we would hope to come from this meeting are new partnerships, new ideas, and we look forward to seeing the outcomes of this workshop. With that. Thank you very much. And I'll turn this over to our keynote speaker. 19:11 --> 19:24

**Jessica Falcone:** Actually sorry we have one more VIP remark, and that is from no, that's all right. I got out of order already from Dr. David Rampula. He is the director of DDST,. he Bioengineering Division at NIBIB at NIH.

19:30 --> 21:28

**David Rampulla:** Thanks. I don't have any movie quotes and I don't actually have any figures, either, that Andrea had. However, so I guess I'll talk for a minute about NIBIB, because we're a really small institute, and you'll hear more about NIBIB from Jessica during the funders panel. However, you know, we cover biomedical imaging and bioengineering. And I think at its heart, we are technology developers, right? We love making new awesome medical devices. And I think arguably a lot of modern biomedical innovations are underpinned by microelectronics. And I think a lot of times we are secondary consumers of the microelectronics industry. Things aren't necessarily fit for purpose. And I think neuromorphic engineering and neuromorphic computing can open up a window to next generation biomedical technologies. And Ralph showed the whole body. So, you know, it's practically limitless. And you know, I think the benefits that we're going to hopefully start seeing, and I think people have already touched on them. Right. There's energy consumption. I think from the health perspective, I think privacy is going to be a really big deal where you can compute on chip and say, it gives me you don't have to send it to those data farms as much as you used to. So and another perspective that NIBIB holds to that, I think is a little more forward looking. And I don't know that we're going to touch on it a lot here, but neuromorphic computing, I think, offers the possibility of communicating directly with the biology in the human. And so it could open up new ways of engineering biology for human health. So that's kind of really all I wanted to say. I'm so glad there's lots of disciplines in this room. I think this is the way we're going to move this field forward, and I'm really looking forward to the next few days. Thanks.

21:34 --> 22:33

**Ralph Etienne-Cummings**: excellent! Which brings us. You know, as you can expect with these kinds of meetings. Right? We're going to be running a little bit late, right? But it brings us to our 1st keynote, which is going to be given to us by Professor Timothy Denison. who holds a Royal Academy of Engineering chair in emerging technologies at Oxford University. He explores the fundamentals of physiological closed-loop systems. Prior to Oxford, Tim was a Vice President of Research and Core Technology for Restorative Therapies groups of Medtronic, where he helped oversee the design of the next generation of neural interfaces and algorithms technologies for the treatment of neurological disorders. So without further ado. I will turn it over to Tim and welcome Tim. Thank you very much.

22:35 --> 1:10:56

**Timothy Denison:** Pleasure to be here. So I reflected on messages I might be able to share that would be relevant for this community and that I know a little bit about. Additionally, so I'm gonna actually do a retrospective of the design of an adaptive brain stimulator that we worked on at Medtronic and just came through its clinical trials. And, I think there are some important lessons learned for this community, one of them being, I would say, not just neuromorphic, but physiomorphic and talk on why I think that's important and why I think this could be generation three of devices.. So I just want to acknowledge there's a large number of collaborators behind this. Both academics within the team, a lot of industry partners, of course, clinicians working together – you see we already ran into Kendall Lee and Syd Cash. So kind of engineering working with clinicians is where the sweet spot is. I think we need to be mindful of that. Additionally, then also some of the practicalities of building things that's actually on in the clean room welding together a can, and so if she doesn't do her job right, you know the best ideas don't come out with some quick disclosures. I do have some links in industry with Cortec Neuro, Inspire, and Synchron. I actually have no conflicts with Medtronic. I've divested of all shares and the like. So I can talk about their materials.

Slide 2 - I did ask my old team for some slides, so they provided them, and with the following 2 critical disclosures which I promised I would share. One is that they did provide these, but they're not sponsoring or promoting the content. And then also, what's critical from the FDA perspective and for any clinicians is that the research devices I'm discussing, adaptive brain stimulation is still limited to investigational use only, not commercial sale. Alright. So let's get started. I'm gonna give you the 4 slide overview, and then we'll get into some details. So a snapshot of bioelectronic therapies and practice in 2024. We're actually at a very exciting time I think where we're going from what's been historically for most neuromodulation systems, what we call these open-loop systems. So these open-loop systems which are actually not open loop, there's a clinician who's actually in the loop. It's just it's a very under-sampled system, so they'll come back every 3 months, say, at Oxford, and there'll be a fine-tuning and titration. As we're entering the 2020s, though there's been, and actually a lot of this funded by the BRAIN Initiative. This moved to the state of the art where we're looking at a physiological marker. And then we can actually look for that correlation to a symptom change, or a patient state, and use that to adjust the stimulator in real time. However, there are some engineering and clinical problems. I'll touch on these first. As of now it always seems to be daylight in the brain-stimulation world. So let's talk about what that might mean. Also, any closed-loop system can become unstable. And so how do we balance stability with its error tolerance? And also core to this conference is power consumption. How do we actually implement these systems without undermining some of our design requirements for patients?

Slide 3- So what really kicked this off in my space in Parkinson's Disease and Movement Disorders was a seminal paper by Peter Brown and Simon Little that came out just over a decade ago. I'm going to walk you through the mental model. Which is, that they saw a correlation between the power and the Beta band around 20 hertz in Parkinson's patients measured off the DBS electrodes. We could sense that off of no new implant, but actually, from those electrodes around the same stimulation electrode. And just like a home thermostat, we look at the power and the power hitting above, going above a certain threshold was indicative of and correlated with, the patient showing their Parkinson's symptoms. So you detect you've crossed that threshold. You gate the stimulation on And they ran a very interesting trial where they had no DBS, adaptive DBS, continuous DBS And then to demonstrate it wasn't just the pattern of stimulation, they ran that train of stimulation asynchronously through the brain and showed actually worse performance. So something like in some of the responsive epilepsy devices today, this has not been done. So they actually showed that there was a true mapping between the physiological signal and the stimulation pattern. There are very few areas of physiology that respond like this on a threshold, whereas a tipping point is where you cross a threshold and then bam you immediately do a discontinuous change of state. Is this the best algorithm? Probably not. And we'll come back to this. So lessons learned, I'd say this is not necessarily the best way to go forward.

Slide 4 - The other thing I'm pointing kind of laughing at my Oxford colleagues is a lot of these studies were done between noon and teatime, because that's when we have the lab available in the hospital to do these measurements. This is when we have patients coming in for follow up. What are the implications of this in the Circadian rhythm space? It's the peak of your motor performance. What does it mean if you actually are basing all of your adaptive research on a snapshot in a specific time of day? We don't even have a nap captured in that initial data. What does that mean? How is the brain different during naps during sleep versus the time of day.

Slide 5 - So one of the big pushes that we're working on in our group and is really tied to the themes of this conference is thinking about devices that model and restore physiology. And this goes back. These are not my words. This is actually going back and reading the literature from decades ago, where it's not just reactive stimulation, it's also predictive. And how do we merge our ability to predict what's coming in the future with what is happening instantaneously, and use those together in some way to optimize the care of patients with new devices, and that gets into this notion of physiomorphic in addition to neuromorphic, just thinking about how physiology does this. So the example I give to make this salient, I keep bees. So bees, if they just reacted to the instantaneous pollen in the spring flows, they wouldn't have enough bees available to take benefit. So we're going into the wintertime in Oxford, too. The bees are actually all dying off. They'll go to a low-level limit. and then right around the winter solstice, they get a cue from daylight and the Queen starts laying eggs and building up the hive and it's actually at risk for them because there's no food available. However, they're building up their colony with that synchronized through evolution to maximize that when the spring flows hit, they have a critical mass of bees to take advantage of it. And so in the absence of prediction in biology, the bees would die, but they've evolved to take advantage of this. So I want us to think about both predictions as well as reactions in our future systems

Slide 6 - Alright. So now, that's the 4-slide overview. Now, I'll get into some details. So one of the challenges we have in my space of neuromodulation as we look at the number of patients that we're serving today compared to the opportunity. And so this is a snapshot from about a decade ago in the EU, of the number of people suffering from a disease in a given year, the cost per subject in the middle row in Europe in euros, and then the bottom row is the aggregate cost for that disease state. So right now, the state of the art and neuromodulation for DBS is still Parkinson's disease. We have modest penetration even with the advancements we've made. So one of the things we want to think about is how we improve the care of patients and Parkinson's and increase the number of people we're serving, but also at the same time, look to transfer this technology across to other disease states that actually might even have a greater societal impact.

Slide 7 **-** So I work within the NHS, National Health Service. Additionally, so it's a combination for us, not just of the technology. So NIH and NSF might focus on the clinical necessity of building strong science and technical maturity. However, I also want to have a message for this group, as we need to think about some of the practical elements, such as the economic viability of our approaches. What's the workflow? And I'll come back to this a little bit. It's kind of why we configure devices between noon and teatime? It's convenient. So what do we have to do in order to expand our workflow, and also think carefully about the regulatory pathway.

Slide 8 - So some of the themes within my team and we'll come back to the slide over and over again, actually has some similarities to what we saw earlier from Ralph is that we look across the different disease states that we might have an impact with bioelectronics going from the brain to the heart to the periphery and think about an opportunity for a common technology stack, or at least, being mindful of what the building blocks are for that stack from the material interfaces and the actuators to the same or different interfaces to sensors. How we link those together is with classifiers and control policies. Additionally, of course, how we can actually train those algorithms and create the database that enables those.

Slide 9 - So even when we have such a technology stack, this comes to the regulatory pathway. We have to think very carefully about how we explore new concepts. One of the big issues in novel bioelectronics, especially in devices, is the chicken and the egg problem. When I was back at Medtronic we'd go to our executives and say, I think that adaptive DBS for Parkinson's might actually be a great move forward. Well, how do we test that? Well, one thing is to build a device completely from scratch, which costs up to a $100 million plus dollars and then running the trials. So they say, well, that's a lot of money to take a risk on. However, we don't actually know the opportunity until we build such a device. And so one of the models of our team has been thinking about research tools and kind of calling them science payloads where we can take an existing platform that gives the guaranteed therapy to the clinicians, the patients that convinces the regulators that there's a base to build on and then once the patient actually assigns themselves and opts into the trial, we can unlock these novel characteristics in the science platform. Researchers such as those in the BRAIN Initiative can then explore new concepts, look for biomarkers and the like. And then the great thing about modern technology is, it's upgradable. So any of the innovations that we find if we can implement those in the existing hardware, those can be the basis for the future. So one of the notions is we do these platforms well, we can kind of incrementally move forward and still have profound benefits. So that's one of the tradeoffs. To be honest, it's more of an incremental approach than say a breakthrough, but it served me well. So everyone has their strategies, none of them is ideal. That's just how we've gone forward.

Slide 10 - But as an example of how these science platforms can be deployed. One of my favorites is with [Gregoire Courtine](https://pubmed.ncbi.nlm.nih.gov/30382197/), who's at EPFL and his work in spinal cord stimulation. So the reason I like to highlight what Gregoire was doing is, he was interested in spinal cord stimulation in the spirit of neuromorphic processing. He was looking at novel patterns of stimulated stimulation applied - so much more advanced than what you get with say a typical chronic pain stimulator for low back pain. However, we could actually implement those patterns with a simple firmware update. So literally, one firmware engineer sat down and spent a few months rewriting the code and then with telemetry commands in real time, we could sequence through those patterns with external sensors or through patient commands.

Slide 11 - And this enabled us to basically prove out the concepts that Gregoire was interested in for spinal cord rehabilitation, reusing a rechargeable deep brain stimulation device.

Slide 12 - And so literally one firmware engineer, less than $1 million dollars invested, and we're able to get to this state.

Slide 13- And so I do think one of the opportunities for us as a community is to think about not just pushing to the most advanced but what can we do to incrementally improve some of the existing technologies today that, I argue, have a lot of hidden capabilities in them.

Slide 14 - So easily said in 2024. Let's roll the clock back 20 years. So there was not a device out. The Neuropace RNS was still in its development as well. And we'd look at these opportunities, we saw hints of the possibilities, but we weren't quite sure how to move forward. And this gets into some of the neuromorphic pathways and lessons learned.

Slide 15 - So we got here just to make sure everyone's grounded using generation one deep brain stimulator, which was inspired, many say, by replacing a surgical lesion. So Benabid was going in as a physicist, he said, I'm going to cauterize this tissue. Now let me actually just out of curiosity, hook it up to a function generator and see what I get. With a patterned stimulation they saw improved tremor control Parkinson's disease. So Medtronic had been updating a cardiac stimulator instead of routing it down into your ventricles, routed it up through your neck, and then a stereotactic neurosurgeon can place those leads into specific targets. Now, my concern was, we as a community choose your words carefully, because when we say it's a reversible lesion, lesions themselves tend to actually come with a static connotation. I think it kind of anchored the field a bit in terms of that choice of words.

Slide 16 - But this gets into the NSF point: energy! So we have to like, let's put a stake in the ground for energy. So what are we talking about? We go back to our tech stack. Typically, these devices run in DBS on the order when I talk orders of a hundred microwatts. So that's the kind of energy consumption we're talking about. If you're interested in cardiac pacemakers, those are one microwatt. And then we have different technologies in between. However, for this conversation order of about 100 microwatts. This was 20 years ago. So when we start thinking about the sensors and classifiers, in order for me to convince anyone to try it, we need to be about a factor of 10 lower or we need a discontinuous change in the therapy opportunity. So if we halted the progression of Parkinson's disease and removed all of your symptoms without side effects, I'd probably be able to put a little more power into my budget, but at this stage, we were literally thinking, it's going to be an incremental improvement over the standard of care. That's what the data had shown. Additionally, so instead, we were saying, 1 10th the power. So we'll get therapy improvements, but without a big addition of the energy consumption and the device that would limit its longevity.

Slide 17 - So this is a slide from my community presentation. So yes, that's a thermostat on the wall. So I kind of give that analogy. We're saying, what is the equivalent of a thermostat? What is the sensor, the biomarker that we can use to control this device? You know. Oftentimes tomorrow we talk about wearables with EEG. We don't suffer from the concern of being implantable because we already have deep brain electrodes going in. For us 15 years ago spikes were still too risky. Just the longevity wasn't there in terms of its measurement capability. It’s still a challenge today. And so instead, we looked at ECoG and local field potential, kind of the ensemble average, and what signals might be available from those ensemble averages measured off of our existing electrodes.

Slide 18 **-** And so even within that space, you can think about the brain states. One is to evoke a potential which has now actually become exciting in the last few years. However, what we were seeing in this space was especially off local field potentials measured from electrodes in the brain. We could see these clear sensorimotor rhythms. So it's thinking about like a radio dial at specific frequencies. We could look at the power and specific bands and use that as a biomarker potentially for adjusting the stimulator.

Slide 19 **-** So there were 2 competing methods at that time. One shown at the top, and this is what I showed earlier was to measure the Beta power against a set threshold and use that to gate the stimulation. So kind of a bang bang! controller, how your house thermostat works. You cross a threshold. Turn your boiler, your furnace. On the other, out of Italy with the Priori group, was to instead do more of a proportional feedback and so looking at the energy in the band, use that to adjust the stimulation amplitude accordingly. So at this time we're still debating and getting the clinical data on which works best. However, both of these had a common need for measuring the beta amplitude and I'll come back to that amplitude being on the order of one microvolt. So one of the challenges in Parkinson's disease, compared to epilepsy and cardiac pacemakers, is that signals are about a microvolt RMS in the subthalamic nucleus down the basal ganglia. So a factor of a thousand less than a cardiac pacemaker. So this is quite a challenge.

Slide 20 - As a graduate student when Rahul Sarpeshkar was getting started at MIT, and we spent many hours of classroom time discussing principles of ultra-low power design. And he's got a great summary paper from 1998, and of course, his textbook. However, thinking about Medtronic, you know. Yes, we can customize electrodes. We were looking at analog preprocessing before we digitized to save energy. Operating our transistors in subthreshold and then looking to balance computation and communication. And Rahul's summary paper is looking atwhere do you have the benefits of analog versus digital. And one of the appeals of the analog preprocessing is that the inherent signal to noise ratio for many of our devices was on the order of 20 to 40 dB. And so that put us in a spot where maybe analog preprocessing is actually a very efficient way to go.

Slide 21 - Now the thing is, there's 1 big issue that we face in an adaptive system for Parkinson. Unlike the Neuropace RNS, our device is generally on in the background. And so there's a big contamination signal flowing and it gets superimposed from the stimulation up to the sensor. And then within millimeters of each other. And so this is a signal that's easily a million times the amplitude than the signal we're trying to detect. . So that's another confound.

Slide 22 - So kind of way over on the right hand side, 120 dB is the stimulation artifact. And how do we deal with that? And so that's 1 of the other constraints we're under.

Slide 23 **-** I'm notgonna to. So I started as a circuit designer and transistor designer. I'm not gonna drag everyone through the weeds. However, I'm gonna have little red marks to annotate this. So we called it the brain radio. And the reason for that is that we actually repurposed Edwin Armstrong's analog super heterodyning approach. So when I talked to the physiologists and the clinicians. So we're just trying to measure power in a band like all you need is an AM radio like this is a piece of cake. So I sat down and just repurposed a chopper amplifier that I worked on for the cardiac pacemakers. We could adjust the center frequency with another independent filter tuned to the bandwidth of interest and then extract the power. Additionally, what this allowed us to do is for about 5 microwatts. We could extract the microvolt RMS energy in a band, then digitize it down at the one Hertz level. So we ended up at 5 hertz, but that then allowed us to run a microprocessor and kind of sample the spectral energy and use that to adjust the stimulator also for about 5 to 10 microwatts. So we're hitting our energy budget of extracting a microwatt level signal from the basal ganglia running an algorithm and using that to adjust the stimulation.

Slide 24 - So it was a great day. It's the one time in my life I think I ever impressed my in-laws. I got a phone call from John Donoghue, and he said, Can you be at the White House In 2 days? And I can't tell you why, but it's relevant for the work you do. I said. yes, actually, it's kind of funny. Because I went to my boss, who had just started the week before at Medtronic and said, I've been invited to the White House. I don't even know what we need permission for, and he said, I don't know either. And so he said, just go and don't make a fool of yourself. Additionally, so that was when Obama kicked off the White House BRAIN Initiative which has evolved into the BRAIN Initiative. Additionally, it was perfect timing. Because we're just at the state where we were basically taking that brain radio and building the scientific instrument kit and putting on top of an Activa PC stimulator. So we're ready to go. There had been one or 2 protocols that had been signed up for this. And then we ended up, I think, on the order of like 25 to 30 projects just on the Activa PC process alone.

Slide 25 - So thinking methodologically and kind of step by step. You know, step one was to demonstrate off of a device that we could actually measure microvolt RMS signals. So reminder this is about 100 times smaller than the typical, certainly 10 times smaller than a typical seizure that you might see. So a good lead off project, for that was University of Medical Center, Utrecht, with Nick Ramsey, where he put a device, took the Activa, PC, but instead repurposed --this is modularity of platforms -- the spinal paddles from SCS and put them over the cortex of Annika. She gave permission to share her name. She had ALS. and then, by doing the classical of putting the leads over the motor cortex on her left-hand side, she could think about moving her right hand, arm, and hand, and then similar to looking at the frequency and the power, we could actually detect basically tune that AM radio receiver and the device to the Beta band and the gamma and use the variation between rest and attempt state to then control her external computer. We just actually gave the 8 year update on her device. And it's actually a very poignant story, I think, in the [New England Journal of Medicine](https://www.nejm.org/doi/full/10.1056/NEJMoa1608085).

Slide 26 - I think that's kind of one of the messages. Not everything right now is neurotechnology. Keep putting some dollars into cure. That would be my one sentence summary of that [New England journal](https://www.nejm.org/doi/full/10.1056/NEJMoa2314598) paper for those of you at the NIH. So then, once we have that we knew we could build a reasonable brain computer interface. This is when John Donoghue's and others are saying, wellthe problem with BCI today is that we can only do a 1 bit per second control reliably. But you know that's much better than patients controlling their device. So let's take that BCI and link it up to a device and say, use it to control an essential tremor system.

Slide 27 - So this is another NIH BRAIN project with Ayse Gunduz, Kelly Foote, and Mike O’Kane down at the University of Florida. And what they did was put a combination of thalamic stimulation electrodes down for actuation.

Slide 28 - And then the same approach that Nick Ramsey had used for cortical electrodes over the brain to measure intention to move.

Slide 29 - So we'll start out I should say Enrico O’pry is now in Michigan. He would characterize the subjects with the device. So they would have inertial sensors on their arms for objective measurements, have them go about their activities of daily living. This is with the device off. You can see them struggling. And now we would actually tune. So this is what the next part of the movie will show is tuning in. This is the raw electrode. This is tuning the radio into 2 frequency bands 15 and 25 hertz, and the bottom panel magenta is the stimulation state, and red is synchronized with the motion. You can see that as he goes about pouring his glass, and puts his hand down. You get a Beta rebound which can be detected, and stimulation turns off. And then when he goes about his intention to move, the Beta band drops below a threshold. Then we can ramp the stimulation up. So this started to give us confidence that we could take the device, measure brain states in real-time, use it to turn the stimulation on and off, and do it in a robust manner. Ayse published this in Science Translational Medicine a few years ago. Then the last part that we have to think about is that many of these patients that we're trying to help have a combination of a device and pharmaceutical. So this is a gentleman with dyskinesia when he takes his dopamine provided by Phil Starr.

Slide 30 **-** And this highlights the need to think very carefully about how the device and external pharmaceuticals work together. That's definitely a design input. And one of the things that we find in devices is that they can respond, of course, orders of magnitude faster than many pharmaceutical agents. So, if we adjust the relative bandwidths of the device responding compared to pharma coming and going,we can look to optimize the holistic care of the patient. And that's another one of the areas to think about the overall physiology. And also at the same time look at new biomarkers that might be associated with disease. So this is another interesting one when Phil, the nice thing with the research tools is when Phil started to make these observations and said, I've got this half harmonic, and that's clearly a stimulation artifact. And so we debated this for over a year. Like 2 years. Oh, that's just a stimulation artifact, that's a stimulation artifact. However, we had one of those kinds of experimental gifts where the research subject came back into the clinic. The loop recorder was running inside of the device, just kind of recording and storing data away, and then they took their dopamine. and then they went just dyskinetic and when they downloaded the loop recorder, you could actually see the transition of the Gamma band, and how that correlated with the Dyskinesia State in the patient. So that was great, because, as a circuit designer kind of my background, I said, you know, Phil, yes my circuits have lots of artifacts, but they don't respond to dopamine. You know, this is not one of Kendall's sensors. Like this is just a platinum-iridium electrode. It's not going to respond to dopamine. Additionally, so we've actually done a lot of theory behind this since I went to Oxford. However, that's also what's kind of cool is we can actually use this to discover and refine our understanding of biomarkers in a more lived environment so kind of in a chronic longitudinal state.

Slide 31 - So all right, this is about 10 years ago, and we're ready!Everything I showed you we've checked all the boxes. We can do measure the biomarkers. We can do adaptive loops. We can titrate them with stimulation. We're ready to go, right? Wrong. No, this is actually one of the great things with the BRAIN Initiative is one of the challenges among many that we faced is that all those examples I just showed you used cortical sensing.

Slide 32 - Cortex is easy. Sorry, BCI folks. Cortex is easy compared to basal ganglia and the thalamus. Those circuits,the signals are 10 to 20 times larger than we were seeing in the basal ganglia. So we really struggled to get the sensing during stimulation and the resolution of the biomarkers to work subcortically. And that's where our electrodes go for the mainline therapies. So we had to patch up the sensing and the stimulation. The other thing is, we weren't convinced that the algorithms were really fit for purpose. Yet we're seeing hints of this actually with Helen Bronte-Stewart at Stanford, who is also funded by the BRAIN Initiative. We're thinking, maybe actually, multiple thresholds are more appropriate as opposed to this bang, bang! You go from off to fully on and jumping around. Is there a more subtle way to go about this?

Slide 33- This gets into my point on physiomorphic, and actually very much to the early point about getting from hardware to thinking more holistically about algorithms. If you go back and read the classics. Especially for the students. My theory of all this technology is that every generation basically reinvents the same thing over and over again. It's just we run out. Either we're successful or we run out of gas, and we don't talk about it anymore. However, then, usually, a generation goes by and the technology has shifted enough that you should revisit some of these old ideas because actually, the time might be right. So 2 points back was a high school student, Houk put out control strategies and physiological systems. Additionally, he pointed out, that we don't just rely on feedback. We also have feed-forward. As I mentioned earlier, we can make predictions. You can probably predict when you're gonna have breakfast tomorrow, your body has a good estimate for that, and it will take advantage of it. And they also have these slow adaptive controllers. And if you really go deep into the old literature back to Walter Cannon from homeostasis. He never wanted to say that homeostasis is a simple set point. He said, the purpose of homeostasis is to bound you within acceptable limits. And so this is an example of glucose and how it's impacting your body and your liver is going to kind of sit and let it flow beyond a pretty wide margin. It's not sitting here saying, I want you to sit right at 100, I'm gonna let you go between 70 and 130, and those are tolerable limits. So instead of taking this, this is the set point for your brain. Let's pin it to that value. Let's actually define some upper and lower limits. Additionally, then, when you're in those limits, let's just let the brain do its thing.

Slide 34 - So that was the next generation device which became actually a real workhorse for us at the BRAIN Initiative called the Summit RC+S. It was a rechargeable version, but also with a completely new chip stack. So I'm not gonna - the key points from this new chip stack was that one we moved from the analog preprocessing to actually using an on chip fast Fourier transform, and this dropped the power down to 250 nanowatts per channel in order to do the extraction, and we can measure all the bands in that in that window, and not just measuring one or 2. The other thing is, we ended up with a state transition table. So just like Walter Cannon, and the idea of homeostasis is, you set a lower bound and upper bound, and then an in-range so take no action. You know, if you're in range, what do you do? And we could actually make across multiple dimensions, have this act a little bit more like the theory of Cannonbut also how much of your physiology works. Then we also have all these little mysterious boxes planted around.

Slide 35 **-** And that's something else I'm going to come back to is risk management. So when we're talking about neuromorphic systems, physiomorphic systems. How do we work with the regulators to do appropriate risk management and show that our new technology is safe? And so there are standards for this. Ayse and I took her example from the BCI controlled thalamic stimulator and wrote a little tutorial on [60601-10](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-medical-devices-physiologic-closed-loop-control-technology), which is physiologic control. Safety systems starts out baby incubators, drug pumps. Kind of there's a uniform approach that we can take where we go from our blue boxes, which are a classic closed-loop system of the patient, sensors, controllers, actuators, and the clinician is the command transfer element. This is regulatory speak. And we supplement those with the tan boxes: actuation limits, upper and lower bounds, fallback mode. So if something goes wrong with that control loop, and the patient needs to disengage it, that they actually go. The device goes to a known state and being very careful about physiologic dynamics, not basically having too much loop gain, and perhaps having the patient go unstable. So these were also embedded in part of the summit RC+ system. And that was a great. It created a sandbox if you will. This is for the innovators. Is it in a combination at that time with the our FDA partners with the BRAIN Initiative. With these safety systems in place, it created a sandbox where we could explore new algorithms. And so they felt confident we would limit or contain any potential patient harm to a known state. Then once we had the safe sandbox in place, then graduate students could try out new ideas and kind of push things forward very much like the multi-threshold stimulator algorithm I talked about.

Slide 36 - So now I'm going to go over. You can see these look a little more corporate. So these are some of the slides provided by Medtronic. So this is to kind of bring it all home on this 20 year journey, as they've just wrapped up the adapt PD Study, and so the intent was to demonstrate the safety and effectiveness of adaptive DBS with patients with Parkinson's. I'll get into the trial design here in a second, a sample on the order of 70 people, with an additional 20 in the directional cohort. These were patients who had a Percept which is basically the next summit RC+S, the commercial version of the research tool. And we could work across 10 sites across the US and Europe.

Slide 37 - So what I like about this is I think we're in a time now, also, in terms of the neuromorphic / physiomorphic. I call it the battle of the algorithms. And so we can have different devices trying different algorithms and running them off against each other. One of my business goals when I was still at Medtronic, was that we treat it like an app store. So different physicians would try things, maybe funded by the BRAIN Initiative, and that would be their algorithm. And we could monetize different algorithms. So you could say, Oh, I want the you know, I want the Bill Stacy algorithm for my epilepsy device. I want the Chris Rozell Mayberg algorithm for my depression device. And we could create this community of people who would explore new algorithms, and we can give them a pathway that they can monetize their ideas. And we could get it out there. That's still my dream. I haven't given up on it, but we can at least get started by comparing 2 threshold, 2 algorithms. So I call this call this sometimes the single threshold. That's the Bang! Bang! Controller, you know [Peter Brown and Simon Little's](https://pubmed.ncbi.nlm.nih.gov/32039501/) fast adaptive approach. So it stems off and goes full on or certainly a lower limit. And then the dual threshold mode, this is more the homeostasis of, you know Walter Cannon's idea. Yeah, we got 2 safe operating zones, a lower limit and upper limit. If you go too high, we're gonna turn the stimulator down. If you go too low, you go too low. We're gonna turn the stimulator down. If you go too high, we're gonna turn it up. But then we're gonna let you wander around. Your brain can do its thing.

Slide 38 - So the way the design of the study went, the patients would get enrolled. They would get their continuous DBS. That's what I like. So it's like there is an accepted standard out there that's been there for decades. You've got to show you're better than it. So you get a sense of where patients are over about a month with their continuous DBS. Then you'd start to characterize their, the patient's, physiomarkers, such as that Beta band. Then they would get randomized. and you compare a 2 30-day blocks: adaptive DBS with the dual threshold. So the homeostatic approach versus adaptive DBS with the bang! bang! thermostat approach. And so mix the orders and at the end see how well we did then, of course, long term follow up.

Slide 39 - Apologize for the eye chart there. This is available online with Helen Bronte-Stewart and abstract just this year. But, you know they did as I said, the 68 participants went through. One of the challenges is the biomarker there and the majority of patients that was there, and they could show that at least one adaptive mode was feasible.And about 90% of the patients and 30 were actually tolerant to both modes. So the primary outcome was achieved with similar on times without troublesome dyskinesias. So that's the video showed with Phil Starr patients taking their medication. However, what I find interesting? Why, I bolded it. I said, if we had gone with the original idea from a decade ago --so pre-BRAIN Initiative. I'm not just doing this to play to my audience-- I actually do want to thank the BRAIN Initiative for this. We would have gone in. We probably would have won with the one on the left-hand side commercially and it did not meet statistical significance in terms of its impact. The homeostatic side, however, with a dual threshold, did meet clinical statistical significance and outcomes, basically doubled the impact that we saw with the single threshold model. So for me, I don't want to overplay it, because there's some technical limitations of the single threshold. We haven't fully refined things. However, for me, one of the takeaways is it makes me wonder if we look at the when we're designing algorithms in these device systems, f we look at how the body is naturally responding and adjusting its servo algorithmsand we try to mimic that. Maybe that's actually the way to go forward: physiomorphic neuromorphic for us as a community is thinking very carefully. Yes, we do things as engineers like thermostats and I'm just as guilty as the next engineer. We pattern match to what we know learned in school. But maybe we need to step back and say we're trying to work in physiology. Let me talk to the physiologists, the neuroscientists and clinicians, and refine our way that we go about things.

Slide 40 - So are we there yet? I still would say, no, there's room for opportunity. However, one of the things we have to do is make sure we take credit and get devices out today. You know. In order for people to translate, we've got to get systems out and continue to be blunt. You've got to make cash flows. Companies like Medtronic, Abbott, Boston Scientific have to make some revenue so they can pay taxes. Those taxes then go in and actually fund the next BRAIN Initiative. So we do need to get systems out.

Slide 41 - But I do think we still have one area that's left untouched. And that's the predictive element. Why do I think this matters so? One of the nice things with the Percept, I'm gonna use that as our example, is that we have this mode. When I was still at Medtronic we did a quick back of the envelope estimate. We said, patients are in for follow-up like point 0.05% of their life. And so what's happening outside the clinic? You know. We've got this sensor. Let's take advantage of it and build like a little loop recorder and get some sense of what's going on. So it's still fairly crude. But you gather a 10 min snippet of the local field potential recordings. You do that FFT. The clinician researcher or their engineers work together. They'll define a 5 Hertz band of interest. Let me create a data point. So I mean, it's yes, you know, neuroscientists will howl. You know this like, Oh, my goodness, what's this good for?

Slide 42 - Well, it's good for one thing, and that's that you can measure these over months. And so you can actually get a real snippet of what are the daily rhythms of a patient. I don't think you have to try too hard, if you look at the Beta z score. So the Beta band energy with a z score over time is about a month. You see this daily repetitive motion kind of thing and you can plot it as a rose plot. And what you see is basically when the patients are going to sleep, their beta band is significantly suppressed. Now, if you tune the filter wrong,you can get sleep spindles and then you actually see some interesting sleep structure. But then you get into the next part of it. Well, what happens if you start to do adaptive stimulation based on someone's sleep spindle? Is that good or bad? Interesting topic, a future R01 for someone. So the key thing, though, is I think it's funny. We spent a lot of time, a lot of money, we built a lot of circuit chips to measure local field potentials. And in the Parkinson's cohort, 30% to 60% of the variance in the Beta band is just time of day. So a crystal oscillator clock costs about $1 to implement. And if you go to your community neurologists, which ultimately for the BRAIN Initiative to be successful, we need the community neurologists across the United States and the world also understands what we're doing. Most of them understand that there's day and there's night. Additionally, then maybe we should be adjusting stimulation slightly differently during the day versus the nighttime and that maybe we should be adjusting stimulation slightly differently during the day versus the nighttime. So that's where I want to get this predictive element back in. And the other thing that, I think, is important about it from a translation standpoint is that patients have complained about the adaptive mode being on at night, and part of is that their stimulators are actually turning off because they've lost that beta band which you see in this data. However, we know that from the anecdotal and some of the small studies that patients prefer to have stimulation on at night. So I think the next generation needs this predictive element, and the device needs to have a slightly different algorithm going at night versus during the day.

Slide 43 - I'll start my wrap up. That's just my general call for the field. We see rhythms and epilepsy, we see rhythms and pain. I do a bit with incontinence at a spin out. We see strong Circadian rhythms, and it's well known in incontinence. And so what can we do to bring in more circadian rhythmicity into our device design?

Slide 44 - So in the near term, I'd say, here's now I'm gonna get into the creative conflict. Kind of set up the workshop is that in the near term there are some very profound customized chips coming out. This is an example from a friend, [Rikky Muller](https://www2.eecs.berkeley.edu/Faculty/Homepages/rikky.html), at Berkeley. This is a seizure detection chip with some embedded machine learning inside and it gets into the partitioning. So I think when we apply the neuromorphic approaches, we need to think very carefully about the competitive opportunities of more classical signal processing on just sub micron, tens of nanometers of DSP, and where each of them play against each other. I don't think it's an either, or I think there's going to be a combination of the 2 approaches that will ultimately give us the best performance.

Slide 45 - And this is part of my reason for thinking that. I did have a graduate student apply to tinyML, just out of curiosity, basicallyuse tensorflow, and you go through TensorFlow Lite and put into a microprocessor. And yes, he can match the performance of the classical radios that we had these kind of analog, preprocessing steps back from Rahul Sarpeshkar's collaborationbut for lots and lots more energy. And so let's get back to this point of energy, energy, energy. I think we really need to think carefully about how we partition the algorithms and doing an energy efficient method. And right now, just brute force TensorFlow and mapping it to microprocessors is not, for me, showing much benefit. We need something a little more creative.

Slide 46 - But to map, just to wrap, I've got a few pointers for the workshop. So opportunities I hope, especially going through the journey and with the clinical study data coming from adapt PD, that by using neuromorphic and physiomorphic approaches, we can get better outcomes for our patients, which is ultimately what it's about. We have power saving opportunities that are tangible and practical in today's devices. Still thinking carefully about the partitioning, analog, digital. And then also how do we do the digital versus, you know, submicron DSP of quotes versus neuromorphic. I also think there's some short-term wins for adding prediction into what we do.

Slide 47 - Some of the challenges on neuromorphic and why we stepped a little bit more into classic DSP. It's not the stuff that gets you into Nature, but it's designed for manufacturing, test, reliability. Our challenge of microvolt micropower analog processing is that it drifted over time, so we had a lot more calibration steps that we'd have to do in clinical visits than we would otherwise using just classic DSP. Thinking carefully about system verification validation. This gets into my colleague Chris's points on explainable AI and the like. How do we actually go through verification validation with some of our potential architectures? Risk management is the existing approach to closed-loop devices. Is this enough? Probably is actually. And so how do we create that sandbox where we have comfort to explore neuromorphic ideas, even if we can't fully explain them yet? And then one of my key takeaways is don't overoptimize on one dimension. So that's why I gave you, you know, DBS today is 10 to 100 microwatts. So I talked to Rahul about this. So I cherished our friendship. But he'd say, Tim, I can do the signal processing with like ten nanowatts. I said, I don't care. And the reason is I can get a very robust system for an order of magnitude more than that. And I don't need to do it at that level of power. So being very careful and looking at all of the power opportunities and making sure that you're addressing it with the systems mindset. And that's where I do think there's opportunities, especially for large scale parallel processing or more complex algorithms. Everything I've shown you so far is very crude, very crude in terms of algorithms.

Slide 48 - But ultimately, you know, for me, the aim is to really work towards devices that model and restore physiology and of course, for the betterment of our patients. So with that, thank you.

Ralph Etienne-Cummings: Thank you, Tim, for a wonderful talk. So we have time for some questions, if you don't mind. There are two microphones on either side of the room, if you don't mind stepping up to the microphone, because that'll make it easier for folks names. Say your name when you when you stand up and ask a question, please. Questions. Thank you. I have a question. Yeah. Please, if you don't mind, just to make sure that everybody hears it. Okay.

1:11:35 → 1:12:10

**Sydney Cash:** Thanks for a great talk, Syd Cash from Mass. General. An issue that I think will probably come up over the next 2 days. You talk about lots of things really important. You talk about the power, you're talking about analog and digital as part of that decision. I’m wondering if you can comment a little bit about on and off chip. So one of the things that comes up lots of all this wonderful computing power that people in this room and elsewhere are working on trying to get it, you know, shrunk, put on a chip, etc. There's the opposing possibility of just get the data off. Do it all in the cloud, or whatever. Can you comment on that dichotomy a little bit, and how that fits into your thought process here?

1:12:10 → 1:14:08

**Timothy Denison:** Yeah, this is the I was already trying to fit10 pounds of potatoes in a 5 pound sack so thank you for asking the question because I had to cut that. So in terms of this system distribution, that's another degree of freedom that I think, is fantastic and could be more fully exploited. My, so that's my disclosure. I work with Cortec. They've got the brain interchange, and their device is actually designed to do that. They stream all the data out, you run it on a processor, you stream stem commands back in. So from 1st principles, it was designed that way. And the reason I point that out is the latency of the loop delay is actually really important for us to think about with those kind of systems. The colleagues at Mayo Clinic, Greg Worrell, he took the Summit RC+S and he had an embedded, simple, crude algorithm that would respond quickly. Then he would also stream data out. and he would run an algorithm.Basically a tablet that the patients would carry around. And then he had a 3rd algorithm kind of slowly running in the cloud. So on, chip, if you will, near with the patient and the cloud. So the issue. So yes, it's a fantastic opportunity for algorithms. The one thing we need to really include in this is our, we'll call them. lived experience experts, aka research subjects and future patients is, how do they feel about keeping track of all this technology? And so that's one of the things I think we need to think about is how close do they have to keep it? You know, one of the issues with the radios is that sometimes people turn over at night and they'd lay on top of their device, and then the link would drop, and or the bit error rate would skyrocket, what do you do in those situations? And so I think, thinking through the how the device can go wrong if we lose the link, the burden we put on patients. Those are, some of the downsides. But I also think there's some significant upsides as well in terms of you can do a lot more external, but it does come with the cost.

1:14:12→ 1:15:14

**Duygu Kuzum:** Thank you. It was a great talk. This is Duygu Kuzum from from UCSD, one of the organizers of this workshop. So my question is about the neural signals. So you mentioned a lot. Local field potentials. Local field potentials are the most vaguely defined and complex signal in the brain. So they're local. Or maybe they're not local. Right? They're like a spatial temporal average of everything going on, and their information content highly depends on how they are measured. For the case of like DBS electrodes. They're relatively large. There's a lot of spatial averaging going on so that would directly impact the hardware, the detection, the noise, and also the algorithms. Right? If the biomarker is hidden within 100 other things. So it would be very difficult to extract that information. So what are your thoughts about that innovation in how we actually interface with the neural tissue could have an impact on all these adaptive DBS technologies or other implantable devices?

1:15:14 → 1:17:05

**Timothy Denison:** Oh, yeah, I was gonna say, don't get me wrong. I'm not saying LFPs are it. It's more. That's why I also say, going back 20 years,those are relatively reliable from long-term signal recordings. So Neuropace has seen the same with their systems. They are prone to artifacts. So one of the things that I had to pull out of the slides is that a significant number of patients, when you put the device in the pectoral region, actually pick up ECG artifact because it's a thousand times bigger so that can cause confusion in your algorithms and throw it off. If you're not careful. In the short term, there's new directional electrodes that take the existing rings and break them up into threes or fours depending on the company. So it gives kind of not quite an order of magnitude, finer resolution, but certainly a factors of roughly 4 better resolution of what's going on in that local tissue, and that's being taken advantage of, but also creates new technical challenges in terms of just impedance, mismatches and stem artifact coupling in. And so long term there I definitely could see a role for the single units and other measures and other sensors that could come in. But for the next few years, I'm big on taking the most of what we can with local field potentials and doing the most with them. Now this I can see you're frustrated with me. I think maybe I've been kicked around so long doing devices that's like it makes you a very humble, humiliated person. And so I'm not that strong like saying this is it. I'm saying, that's my personal strategy. It has weaknesses. I absolutely accept that. It has weaknesses. But I also think there's a lot we can still extract from what we have today technologically, that's my personal bias.

1:17:07 → 1:17:20

**Joseph Monaco:** Hi, thanks Tim. We have a question from Zoom, from Tobi Delbruk. He asks, are there viable prospects for detecting and quenching focal or widespread epileptic seizures? If so, what's needed?

1:17:22 → 1:18:48

**Timothy Denison:** Yeah, well. Bill's coming up next. So yeah, I'm not gonna take any of his thunder. I think my one observation. So I actually am going to kick the can down a little bit. However, I think we need to regroup. I would say we need to regroup a little bit as a field and come at epilepsy with a fresh perspective, both in terms of the target choices. .What I'm most experienced with is the anterior nucleus of the thalamus (ANT) for the [SANTE](https://pmc.ncbi.nlm.nih.gov/articles/PMC4352097/) trial at Medtronic. So this is one where I will admit to like there are weaknesses to strategy. It pulled off of vagal nerve stimulation cycling parameters, stimulation settings from Parkinson's device, and a new network and a new disease state, and it's also been shown to sometimes corrupt your sleep states as you're turning on ANT at night. And so I think that's an example, where some of our historical reliance on technology might have tripped us up. And the RNS thinking of the brain like we're going to do brain defibrillation once you actually get to a certain level of seizures. Has the horse already left the barn, and it's too late to actually take effect? I think that's how the algorithms are actually being set up and biased these days in terms of just lots of false positives. But that actually might be core to the way the therapy is working. So for me, when it comes to epilepsy, I'm actually in the mode of actually stepping back and doing some more 1st principles. I'm trying to understand how to do a better job of it.

1:18:50→1:18:50

**Ralph Etienne-Cummings:** One more question before we break

1:18:54 → 1:19:21

**Sihong Wong:** First, thank you very much for the very insightful talk. This is Sihong Wong from the University of Chicago. So my question is more about the hardware aspect. So for the circuit chip that performs the full neuromorphic analysis of the signals doing vision for the future, it's better to be wirelessly communicating with the sensors or actuators or stimulators, or it's better to be implanted together as a part of the system?

1:19:22 → 1:21:02

**Timothy Denison:** Yeah. I avoid the word better for anything. So it's so I'd say, yeah, it depends. It depends on what you're trying to achieve. I think this is fair to say. You know, if Gert was here he'd correct me. But anyone else can, too. I think that the problem with radio telemetry is it's still relatively expensive compared to on chip computation. And so the other my bias. So the other way to answer, where do I spend all of my time on the [DyNeuMo](https://pubmed.ncbi.nlm.nih.gov/33692611/) studies which I didn't have time to talk about it. It's training families how to do recharge. We don't talk about neuroscience. We don't talk about, you know, algorithms. We basically do recharge management and keeping track of external peripherals. Now, that doesn't mean that that problem can't be fixed, but the combination of always having some instrument close by telemetry generally will always require recharge, at least in terms of the telemetry approaches I've seen, and the battery chemistries of today. And so I would still like, when I offor my personal bias, is to continue to try to put more and more as we can inside of the device within the limitations. And then maybe in some cases we'll have a distributed loop. I think we have to think very carefully about what the user experience is like and what the implications areif you break that link. And part of that is just the telemetry penalty, objectively, is like an order of magnitude worse than many of the on-chip algorithms. And that's with today's technology, let alone what neuromorphics might bring about.

01:21:04--> 01:21:32

**Ralph Etienne-Cummings:** Thank you. Thank you. And some of the published literature basically talks about 80% of the power being used for telemetry is very expensive. Okay Well, let's thank our speaker. Thank you so much. A little bit behind again, as I indicated. Please go out and get some coffee. Come back. Hopefullywe'll come back at 1035 instead of 1030, a little bit more time to fix, and then we'll go from there.