**Session 1**

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**Grace Hwang:** Welcome back. So we have more tables and chairs in the room for folks that are sitting in the back. We've brought in more chairs and tables in the room. So people should feel free to relocate. We did this all. Okay, so and if you can't see the screen, please log into zoom. The password is Npbh. 2024. I realize some of the new seats we brought in has a slightly off angle to the 2 screens, so you might want to log into zoom to enhance your viewing experience. Yes, the conference Wi-fi is Npbh. 2, 0 2, 4. Yes, there is a conference. Wi-fi. So please, please. So thank you very much for this attending this conference. This is session one, and we're going to go. Do a deep dive into epilepsy in deep brain stimulation. Additionally, also I don't want to leave out motor disorders in Bci. You will be 1st hearing from 3 speakers. They will give a succinct 15Â min presentation with up to 5Â min of Q&A, and then we will invite 5 panels up here to give us their position and thank you give us their position on the topic of the day. What are the needs, challenge contributions, impact investment opportunities in the field of neuromorphic technologies or physiomorphic technologies in medicine. So oops. Sorry. Now, at this point I'm going to introduce our 1st speaker, Dr. Sid Cash. He earned his P. Oh, I'm so sorry. Bill Stacy, my bad. he earned his Phd. In biomedical engineering as well as his medical degree from Case Western Reserve University in Cleveland. He is a current Nih and NInds grantee he runs both. He runs a Eeg. He does clinical research clinical work, and he has his own lab, and he's going to tell us about high frequency oscillations today.

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**William Stacey:** Alright. So I have to be really fast. Because I thought I was talking about one thing, and then they told me, there's another thing I'm responsible for, and then another thing. So 1st I have a license agreement. anitas epilepsy is extremely common. one in a hundred people have it, and 1 3rd of them do not respond to treatment. It is a devastating disease and one of the things that's very challenging to us is that we don't really understand how they start. We don't really know how to treat them. and what I'm going to be talking about today is one specific there. I would like to get that off the screen. That's a possible focus on intractable epilepsy. Those that do not respond to medicines so I'm gonna be doing an impossibly quick review of a surgical case, a ridiculously quick review of devices, and then talk about my own research to start off with. I want to do a very brief demonstration of what we do when we have a surgical epilepsy case. So we see things. These are scalp. Eeg. We would look at these scalp Eegs. We'd see some abnormalities try to identify where we think the seizure is coming from, and by looking at these very, very limited pictures. Then combining that with some imaging, try to figure out where to stick electrodes and the electrodes we put in this is, we're proud of this. However, I've since learned that almost everybody does this. So it's not really all that impressive. This is one patient that I chose at random, and every one of these things is a bank of electrodes that are pushed through a tiny burr hole in the skull. Each dot, you see, is a platinum-iridium channel. and this particular patient has about 200 electrodes on both sides of the brain. You can see we really didn't have any idea where his seizures were coming from, because we're sticking electrodes all over the place. We'll stick these in record 24, 7 for about 10 days. and then pull them out and decide if and where we can resect to try to remove what we call the epileptogenic zone. That decision is very difficult, and it is based on a bunch of empirical ideas. So this is extracted from the surgical presentation that we gave for this particular patient you show a list of where the channels are just kind of still frames of each of these things where they are, and then we show the intracranial Eeg. Additionally, there's different types of things that we see, and this is an abnormal pattern known as paroxysmal fast activity. Here it is blown up a little bit, we can see which channels it's arising from. We see different activities in different areas. You can see there's a lot of data going on here 10 days of this. What we're looking at here is 4 seconds of Eeg, you imagine trying to look at 4 seconds of Eeg over 200 channels. It gets to be very hard. All of that is done by eye. All of that is done from teaching that the person that taught me was taught by the person in front of him, was taught by the person in front of her this chain of empirical ideas seeing if the patient gets better when we cut something out. In this case the person had seizures on both sides, and so we gave him a neuropace device which I'll talk about briefly as well. These neuromodulation devices were never optimized. I'm going to show several of them. and the jazz is knocking me off a little bit here. Yeah. I'm gonna I'm just gonna chill a little bit. Okay. Alright, it's never as good as definitive surgery. Alright. So the 1st device we had was neuro sorry was the vagus nerve stimulator works by unknown means. The stimulation was chosen, chosen completely by random chance, and it kind of works in some patients the deep brain stimulator that Tim showed you before. I was very happy to hear that, he admitted. The thing that I've been saying for 15 years that they just grabbed it from Parkinson's disease and grabbed it from this, and just stuck them together and expected to work with epilepsy. it does work in some of the patients. Additionally, then we've also got neuropace which took the ideas of cardiac pacemakers and combined it with the idea of deep brain stimulators and stuck them together. Additionally, it's a little markable here, though, this is a closed loop device, so that neuro. So the Dbs and vagus nerve stimulator, open loop devices. You just need a battery. Tell it when to stimulate, and they'll last. The batteries last for about 5 years. This is now a closed loop device that senses and stimulates would have a much harder time keeping its battery life. However, it actually lasts 4 years, and the way they did that was by dumbing it down considerably, so that the processing power it has is extremely limited. Nevertheless, they have figured out how to get it to work pretty well. One of the ways they limited it was that they only store tiny pieces of information. This has been a bit of a limitation for epilepsy research that in 24Â h you might have 5Â min of data saved. and it's only from a few channels. They also. really knocked down the resolution of the things that are being recorded. Some other things that are moving now a little bit more to the present day. Tim already showed the Rc. Plus S. There are some ambulatory devices such as the unique. See your medical. There's other things coming along the pipeline of there's a lot of need for continuous monitoring in these patients, even if it's just on the scalp. Additionally, then there's other wearable devices trying to figure things out lots of ideas. Because nothing that we've done before has solved the problem sufficiently. So we're trying to get better data. Going back to what I showed at the beginning. The problem is that the state of the art for clinicians is just not good enough. We keep inventing and adding new things to the clinical pipeline. and it really hasn't made much of a difference. One of the ones. This is the group from Mayo clinic that invented what they call Syscom, which is a subtraction spect. Where they write during a seizure. They try to inject a radioactive tracer. At that exact moment they want to see the area of the seizure lighting up. Compare that with the baseline that should say exactly the area that's involved in the seizure, and if we resect that area, the patient should get better. They did their big case study. They're the ones that invented it and didn't work didn't make a difference in outcomes. I don't believe it. I think it actually helps, but I have no evidence for that, because the only evidence says that it doesn't work. This is our state of the art we keep trying to. I develop new things. Additionally, so one example, a case study of a new thing. This is not the new thing. It's just what what I work on is something known as high frequency oscillations. The way that clinicians look at Eeg is based on visually analyzing these patterns. When we 1st connected these things in the 19 forties. We had no idea what was going to be abnormal. We just looked at people that were abnormal and saw patterns that only happened in them. Additionally, so we said, those things are abnormal. the definition of empirical evidence. Additionally, so we came up with these spikes and sharp waves and seizures and spike and wave discharges. That has been the teaching now for almost a hundred years. But if we zoom down a little bit more to a tech, to a technology that wasn't available in the 19 forties. We start sampling a little bit faster. We can see some things that are not available on Standard Eeg. Additionally, one of these things are high frequency oscillations. They're split up into different patterns known as ripples and fast ripples, and just based on the frequencies. high frequency oscillations. Literally, there are papers going from A to Z, showing that there is evidence between high frequency oscillations and outcome. If you remove the areas that have these high frequency oscillations, the patients tend to get better. However, turning that into a prospective method has been difficult. So this is the type of thing we are trying to do with these. Hfos. This is a standard method here where we would look at where we've placed the electrodes. This is the older style of using grid electrodes. Most people don't do that very often anymore. We fill in all of these dots with where the seizures start with areas of what we call eloquent cortex that cannot be resected. We line all of that information up and then figure out what is possible to be resected. We're trying to add to that information from high frequency oscillations. Additionally, here's a picture of the standard Eeg, that if you zoom way in with a high resolution acquisition, device. You can see these little buzzes of activity that were never seen before. We are extracting literally millions of these things, and then trying to do different big data processing on them to figure out how to use them. The problem is that Hfos. Everything I just explained to you. They also occur in normal brain. and they also occur if your sampling method mischaracterizes artifacts. Additionally, so you've got this combination of Hfos from normal brain, Hfos from artifacts and Hfos from epilepsy almost there. Oh. the problem! If I don't talk, the subtitles go away. That probably wouldn't work. So we have to figure out a way of characterizing what's from epilepsy out of this big mess of lots of different things. Additionally, the problem with that is that there is no gold standard. I cannot ask anybody what is an abnormal Hfo. because all we've done is, look at them. and everybody has a different opinion as to what is normal and abnormal. Additionally, so how do you validate something with no expert markings? Now in the past people have hope, have come up with a very simple idea. They thought that perhaps the faster ones, the ones that were on the high end of the Hfo. Spectrum, which are 250 to 500 hertz. Those might be more specific to epilepsy that hasn't panned out even the groups that were most adherent to that idea when they looked at their data. They just had to admit that it didn't work as well as they. They hoped it would. People looked at other ideas one of the big problems is, it's been very hard to get these, and there's been limited validation. what we've done is try to collect a vast group of these Hfos and try to use data driven techniques to decide what is normal and abnormal. Additionally, we don't have an answer yet. I'm going to show you 3 of the methods we were using to try to find the answer. One of them is to assume that any Hfo that occurs during a seizure must be abnormal. Additionally, so we make a 1 class support vector. Machine of the features of those Hfos and call them Ichtal, like Hfos. and then look to see if we can find any Hfos like those outside of seizures, and by doing that we tended to find more specificity to the epileptic region. Another region. Another idea is to use a umap. This is a sorting method that I won't get into too much. However, basically it just spreads out a lot of Hfos the best it can and and similar Hfos should be close together. We gave this umap no information about patient outcome or anything. and by showing boy that's in a really unfortunate spot by showing red versus blue. We tried to define what we thought was normal versus what we thought was pathological. We got this interesting shape, and and that's the exact shape. They look like kidneys. That means nothing. There's 2 of them, because half of them are positive, and half of them are negative. However, there is some signal here where the pathological ones tend to be in a different location than the normal ones. Additionally, this is, we're looking at over 2 million Hfos here. I think so. There's some type of signal. Additionally, and so we tried to use a classifier training on and doing held out data testing on the held out patient to see if we could build a classifier that could identify normal versus abnormal Hfos on an individual basis. Additionally, some of the patients work okay. and other patients didn't work quite so great. We're still trying to figure that out. So our conclusion is that there is something there, and it looks like there's a pathological signal that we might be able to extract. We've now collected more than a hundred 1 million Hfos, trying to really use a lot of big data techniques. However, it's not been easy. So what we have. This is kind of a a demonstration for this group. We can collect hundreds of millions of events. We can collect terabytes of data from every patient for free and just hand them to anybody that wants to analyze them actually do that with people in my at my university. or I just I just type their name as access to my database, and then they have access to 170Â TB of data that's de-identified. we can do stimulation testing and cortical mapping on these patients. We can look at the response in the brain. There's a vast amount of information that not just epilepsy that can be done with these patients. So these patients are a tremendous resource for people looking at looking at interfacing and understanding brain activity. The word neuromorphic has not been used much in epilepsy. There's only 2 groups that have ever used it. As far as I know. one of them used a neuromorphic chip called the Ibm true North to get a seizure prediction algorithm running on very low power, very real time. Additionally, then another group. So if you're in Switzerland. you can get the government to fund building a chip for $300,000 to do one experiment. That's interesting. So they built this system. Johannes is A is also an Hfo researcher. Additionally, he had his own algorithm and actually just had a paper with a bunch of us. It worked really well. It'd be coming out in brain which is just accepted to brain, where he got all a bunch of other researchers and took their data and just ran his chip on our data, and it worked very well. Additionally, then, finally. so what we would like as epilepsy researchers is, we would like better devices. The devices so far have been extremely limited. Low frequency sampling, low frequency bandpass filters, low bit precision. low capabilities to do any type of computation. All of them are quite similar. There's 1 device that had better sampling over time. They did a seizure prediction device and they went bankrupt. Unfortunately, they're trying to get things going again. and then the bottom line. I don't really care if it's anything that people devise works similar to neurophysiology. Additionally, this is where I have a little bit of maybe disagreement with the term neuromorphic to me. I don't care if it looks like a brain if you build something, I care if it works. Additionally, for me, neuromorphic means, can you morph. the neurophysiology? Can you interrogate the neurophysiology? And I think that has to be done with with high resolution high throughput but low power devices which fits very well with the neuromorphic idea. However, I wouldn't isolate myself to trying to say, Oh, this has to look like a brain just has to interface with the brain. Additionally, so finally, I just like bragging that in one month I saw 2 really cool things in Michigan. So if you're in the right place, the right tools, sometimes you can see amazing things and then like to think these are my collaborators on the Hfo work and that's the end.

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**Jessica Falcone:** All right. I think we're going to move on to our next speaker. I'd like to introduce Dr. Sri Sharma. She is a professor in the Biomedical Engineering department at Johns Hopkin University. She oversees the neuromedical control system lab and is interested in developing computational data-driven and biological approaches to advance the knowledge and treatment of diseases of the nervous system.

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**Sridevi Sarma:** Okay, thank you very much. I'd like to thank Grace and Ralph and others the Organizing Committee to for this invitation. I always know if I'm in a session sandwiched between Bill and Victor. I've made it so. No, it's really a pleasure to be here, and just to to kind of transition from what Bill was talking about to what I'm going to talk about, you know. Bill talked a little bit about his research right where with these Hfos and and this real clinical need to find out where in the brain should they be treating these drug resistant epilepsy patients or epilepsy patients? Right? And so what I've just done for today is I'm going to spend maybe 5Â min like a lightning talk on one of the approaches that we've taken in our lab to analyze the same intracranial Eeg that Bill shares and looks at, and I guess on a daily day to day basis and and show how we use models to try to help clinicians find ways they should be treating. Additionally, then I'm going to move into more. What else do we need? Which I think we need neuromorphic or better computing power when we're talking about feedback control. So I'm going to end there. Additionally, it's going to relate a lot to what Tip was talking about this morning. Okay, so the lightning talk is resting state, eg. Biomarker for seizure, onset zone. So I'm going to start here with a question to you all. So when is a half a brain better than a whole. When do you think? Oh, okay, good one, right? Well, when the other half actually causes intractable seizures. However, I like that answer. So, yeah, so actually, this is a scan of most likely a child or a baby that had a hemispherectomy. So there was a part of the brain that was causing intractable seizures, and they literally remove half the brain. I am told I'm not a clinician, that there are people walking around. You'll never know with half a brain, because it rewires. Additionally, many of these people regain probably what looks to us as a hundred percent function. right, and when the remaining can rewire. So with that said, as Bill was talking about surgery is the gold standard, I have different stats, so I guess it's 50, 60 plus 1 million people in the world have epilepsy. As Bill mentioned, 1 3rd are drug resistant, which means no combination of anti-seizure medications tends to really sufficiently control seizures. Additionally, for what I understand, at least in the United States, there's over 20 plus anti-seizure medications on the market. So I can imagine, as a clinician trying to understand which one or which combination is going to work is tricky. However, then there is that 30% that nothing really seems to work, and surgery seems to be the gold standard, although, of course, we have rns and stimulation strategies. However, the idea is to, if they have focal epilepsy. So the epileptogenic zone or region is sort of focal. You can actually surgically remove that tissue or or cut it, or something to try to suppress seizures. So surgical outcomes vary a lot. they can vary between 20% success to 80% success depending on the case. Additionally, so on average, you're looking at something like a 50% success rate in terms of surgical outcome in terms of seizure freedom, 6 months, one year, post surgery. So lots of people have been out there. A lot of engineers, signal processing computational physics, modelers have all gone out there to say, let's look at this data that the clinicians are visually inspecting, and see if we can compute to try to help them try to find out where this epileptogenic zone is. So I'm going to talk about one of the studies we did on what we believe was a resting State indicator resting state meaning, we are not observing a seizure. We're looking at a few minutes of that intracranial Eeg data can be randomly selected when they're not seizing. Additionally, we're going to try to tell you where seizures start. Additionally, if you use that marker to predict surgical outcome of a plan, it was around 79% accuracy in the retrospective study. So before we get there, let me tell you a little bit, and I, thanks to Bill, he's sort of introduced how clinicians go out there and try to find epileptogenic zone. Ultimately many of the patients go for invasive monitoring where you have electrodes implanted inside the brain. The patient stays in an epilepsy monitoring unit, a hospital room bed for 2, maybe even 3 weeks. Why? Because you have that clinical team, Eeg technicians, fellows, and epileptologists that are looking at the data, and in particular, like many of them look interictally meaning between seizures, for perhaps if they have algorithms like Hfos, or they're looking at what are called interictal between seizure spikes or discharges that could be pointing to where there might be epileptogenic areas. However, most of the time, from my understanding is they rely on the seizure. They look at a seizure event slightly before the electrographic onset and start looking for patterns and signatures that might point to the region right? So one of these signals that you see up here corresponds to a contact that's in a particular anatomical location. Right? So if something's a little off in some of these areas that seems to be pinpointing to where the epileptogenic zone is okay. Additionally, then they do surgery based on not just intracranial, eg. Data, but a lot of other information about the patient. So we built a software tool we call it Ez for epileptogenic zone track. Rs stands for resting state. So it's going to take a few minutes of this intracranial Eeg data and produce a heat map like this. So the red hot areas are going to be indicative of possibly epileptogenic areas. So how do we do this? Remember, I said, we are not looking at seizures. We're not necessarily looking at events like Hfos. We just want to say from resting state data, can I say where seizures start when they do so? How do we do this? We kind of reframe the question for many, many years decades. Lots of people, as I said, went after intracranial ag markers that try to localize epileptogenic zone. What was the question? Well, can I find out where seizures start by looking at a seizure. And, in fact, if you Google, I think my keywords were localization, epileptogenic seizure, onset, computational, ictal. I had over 62,000 hits. That's how much, how much interest is in this field and in this area. However, we changed the question, and we asked 1st of all. Well, wait a minute. If you have an epileptogenic zone which is triggering seizures, perhaps that's what its job is after, because of the disease. Why don't seizures happen all the time. Okay, so if you have this area, that's job is to hyper excite. Why isn't it going off all the time? And we. We didn't come up with this hypothesis, it already existed. However, we thought, maybe it's because other areas that can functionally influence that epileptogenic zone are inhibiting it effectively inhibiting it. That was the concept. So it was an inhibition hypothesis. So in order to figure out how to test that hypothesis, using intracranial eg. Data. We had to define a couple of things about what we call sources and syncs and networks and what our approach here is, we're actually be building models of the network from the data, and then from those models extracting these notions of what I'm going to define sources and sinks to, then hopefully point to epileptogenic regions. So what are sources and syncs? So think of every intracranial Eeg signal as a contact is a node in a network. I apologize the sources. It's not highlighted. We're going to call a node a source if it has a lot of influence on the network. So a lot of outgoing arrows and I'll define influence, but not much influence coming back. That's a source. and the opposite is a sink. A strong sink receives influence from the network, but not is not very influential to the network. Okay? And then, of course, you have everything in between. So sources and sinks are extremes. Okay? So why am I talking about sources and sinks? Because let's go back to the hypothesis that other areas of the brain are trying to inhibit epileptogenic zone. So then, what's happening when you are not having seizures. Well, we believe that in between seizures the epileptogenic zone. it's being inhibited by others, which means not when you're resting state. Your epileptogenic zones are strong sinks that are being inhibited by top sources in the networks. Okay, strong sinks being inhibited. So how do we find epileptogenic zone. Well, if we build a model of the network, we find the top sources. we find the top sinks that they're pointing to that they're influencing. Additionally, then we had an extra criteria. That epileptogenic zone, being a network, has to be coordinated. To have this excited event of a seizure, we find those, and that becomes the hypothesized epileptogenic zone. Does that make sense? Okay, so all right, good. Additionally, so how do we do it? I was told I have to stick to. So let me give you a flavor of the model. Actually, this might transition well to Victor, if he's going to talk about the virtual brain, the models we build are phenomenological. I have, say, 100 signals coming from the brain intracranial, eg, this is a time series, and all we're doing is figuring out through a dynamical system of ordinary differential equations. How are those signals being generated? How do they talk to each other and influence each other? How does present activity of any given part of the network influence, the future dynamics. Okay? And once we have that model which is basically a sequence of a matrices, then we can compute sources and syncs, quantify every node as a source or sync from those matrices. So when you put that together, we can now convert from 5Â min of intracranial, eg. To numbers on nodes that indicate. Are you more of a sink, or are you more of a source? And those top sinks, we believe are going to point to epileptogenic areas. This is our one example, that in our so we tested this on 65 plus patients. This is a nice example. It was the one patient who had 2 surgeries. The 1st one failed. the second one succeeded in terms of seizure suppression. So what you see here is a map, anything that's bright red are these top sinks that are being inhibited by the top sources? So our hypothesis of where epileptogenic areas are okay. Blues are less interesting. So what you can see here is, there's some reds in this area but mainly focused around here. So what am I highlighting in the top red? The top red is where actually the patient went through the whole monitoring procedure, and the clinicians or the whole team treated this area. and they had a failed outcome. Additionally, notice, you don't have strong sinks in that region. However, then that patient came back for a second surgery and through the standard of care they're not using. Clinicians are not using this map right? They're doing what they normally do. They treated this area. Additionally, this was a successful surgical outcome. So it was our one example that we can say, maybe the strong sinks are pointing to epileptogenic areas because we can't prove it otherwise. Right? So we did collect data on, let's see, on whoops. I guess one of the Roc curves is not showing on the screen. However, we collect data on 65 patients that were treated across 6 different centers. We asked every center to give us just a 5Â min random data far away from seizure. We process it through easy track resting state produce these heat maps. Additionally, what we're doing is to we're predicting outcome. So we're saying, Okay, we have these heat maps. We know where the clinicians treated. How much is there overlap between strong sinks in the treated area? If there's a lot of overlap. We're going to predict a successful outcome. If there's not much overlap, we're going to predict a failed outcome. Additionally, now you can see how well that prediction does. Additionally, that's what we're showing here is that our prediction of success versus failure. Additionally, this is sort of the probability based on the model that's using this what we call the sync index. So I was really excited. We published that work. We actually are currently trying to commercialize this. Okay? So now, I'm going to move on to the relevant topic today is okay. We know there's a lot of work to be done on sensing, processing and identifying where we need to treat, where clinicians need to treat to prevent seizures or to stop them or control them right? And there's lots of talk about why closed loop might be a way to go right. Additionally, so I'm going to talk about. Give you kind of 2 sort of closed loop type systems. There's plenty of other systems out there. Additionally, then we're going to talk about sort of challenges, and where neuromorphic computing can come into play. So there's been a lot of work on closed loop preventing via, perhaps closed loop drug delivery. I wouldn't say a lot of work. We are seeing this at the blueprint neurotech program people coming in with really creative sensors and actuators. So one of them that we see is focused ultrasound that can both sense and actuate neurons in a non-invasive way. You can imagine that if you're sensing activity of neurons inside targeted region through focus ultrasound, you can put it through some type of feedback controller. I'm going to call that neuromorphic computing right now and then you can turn that into actuation, maybe a drug release. for example. Additionally, so you have this closed loop system there and then you have. I'd like to put a plug at shout out for the Apl. Our Apl. Cousins at Hopkins. This is technology that was developed by, I think, Rama Venkata Subramanyam, and I think Lou Gosborne and his team here, what am I talking about here? This little thing called a thin fill. Thermoelectric device can sense and actuate, and it can heat and cool, and it can do this at a biologically relevant scales, both spatially and temporally right, it can heat or curl neurons at the order of milliseconds or less. Additionally, so you imagine, if you can, sense activity, maybe from an epileptogenic area. Additionally, then, if it's starting to, if it predicts, or it thinks that there's activity that is predictive of an impending seizure. you can actually actuate by heating or cooling. Okay, but this can be a stimulator. It can be anything. The actual sensor and actuation is less sort of it's not in my wheelhouse. That's not my expertise. Where I come in is this neuromorphic, the computing, the feedback controller. Additionally, here's what I want to say about the feedback controllers. So actually, I was trained as a control theorist, my bachelor's master's, my Phd. With pure control theory. There was no neuroscience in mind, but I was very interested in neuroscience. Additionally, in fact, when I was a graduate student learning control. I was interested in neuro. So I started taking classes in neuroscience. I minored in it. Additionally, I took a class on systems neuroscience with the late Susan Corkin and we and we studied motor system and Parkinson's disease. So I got interested to push my career in this direction because she got Parkinson's disease at 28 years old. After she delivered her 1st and last child. I went to visit her. At that point she was, had been on Levo dope medications for at least 7 8 years. She's already experiencing Dyskinesia, as you show that video right of the Dyskinesias, my aunt, I have the video. She, her Dyskinesias, were so bad that she would literally be on the floor with all this involunteer movement, and it was so bad that her own foot would kick herself in the face, and she'd get nosebleeds like. That's how violent her Dyskinesias were. She ended up with Dbs later, and so forth. Now she's very, very late onset. So anyways, that was kind of where I came in. However, one of the things that my Phd. Advisor had told me before I really moved into the field was, don't lose track of your training. Don't do what everybody else is doing in the field because I was learning new techniques in my postdoc point process modeling of spike trains this and that. However, then he grounded me and says, Bring your machinery to the field. So here's where what I'd like to say here. So we saw. Additionally, this is true, not just in neuroscience, in biological control. When people are coming in and trying to close the loop to treat a disease or something, we've basically seen 2 approaches right? So we saw the threshold control, which clearly, for the thermostat is a beautiful example. Right? The thermostat I actually looked it up was kind of invented in 1620 by a Dutch inventor. I wrote his name down. Cornelius Drebel created an oven with mercury thermostat 1620 threshold based. Now, if you go to proportional control, which is another thing, was or Pid. So there's more sophistication. What are you doing instead of just tracking a signal? See if it goes above a threshold. You're tracking a signal and you're just scaling it. scaling the error. Okay, Pid, or adding integration derivative. However, those kinds of controllers are relatively straightforward notice. Also, they're model free. They don't care what the system is. They're tracking a signal and turning something on or more processing that signal in controls. Things have come a long way. In the 19 seventies and 19 eighties there is a field called Optimal Control, where you can now add energy constraints. Right? So in our case. If you have Dbs, you can actually minimize the energy and track an error or minimize an error of interest. You can control the bandwidth of the actuation signal right optimal control. That was 19 seventies, 19 eighties, robust control being able to. So these are all model based. You have to build a model of the system you're interested in controlling, which can be complicated, as Victor will show you right? So what if no models are right? Right? So how do you control when your model is wrong. when you have uncertainty in your model that's called robust control that was developed in the 19 eighties. Additionally, then, since then there's control over networks. Right? We have the Internet. Additionally, and you have multiple systems communicating with imperfect information. Bits of information is already imperfect. The fact that you are bits now. all right, or even when packets get lost across the Internet, how do you control with imperfect information? So I think these are complicated. They require higher level computation, both in building the models and then building the controllers and then implementing that. So I think that this is very timely, and all I would do is encourage, invite the controls. People invite them. Really, I mean, I'm not. I'm n equals one. Maybe there's my I apologize if there's other people. However, yeah, thank you.

00:43:35 --> 00:44:51

**Grace Hwang:** free for bringing us back to time. So we're gonna set up next, and somebody has a quick question they can ask 3 while we set up next. Almost. if not, I will introduce Victor Gersa. What we set up. So Dr. Victor Jersa was originally trained as a theoretical physics and philosophy. A major in the 19 nineties. He has made substantial contributions to the understanding of how network structure constrains the emergence of functional dynamics using methods from nonlinear dynamic system theory and computational neuroscience. I'm going to skip over his long bio bio because it's on the website. I would say, Dr. Jirsa is most famous for his lead role as a lead scientist in the human brain project and the virtual brain.

00:44:52 --> 01:05:26

**Viktor Jirsa:** That fair. Thank you, Grace, for this great Nice introduction. maybe you can move it to the bottom left. We'll use it the least, I think. Oh, yes, I can move it forward with those excellent. So Hello, everyone. It's a pleasure to be here. As Very sad. I've been involved in the human brain project, which actually just finished in 2,013, and in the Human Brain project. We have also used several neuromorphic architectures. Actually, the spinnaker system and the brain scales waivers those systems. We have performed neuron simulations, single neuron simulations and build networks are out of this. So we need a point neurons. This is this has worked quite well. However, it has not scaled up to any applications in medicine. Additionally, when you look at the last 2 talks, Sri and Bill, there, you saw that we are actually dealing with different type of signals. So we are not on the single neuron level. We are on the level of the full brain and Tim, since you talked about physiomorphic systems. I took the liberty of talking about encephalomorphic systems. Yeah. Which is fully appropriate in this particular context. Additionally, there the entities we are looking at are actually not single neuron spikes. However, we are talking about time, continuous evolving signals. Lfp, local field potential was mentioned earlier. Additionally, what we are interested in is actually, we have mapped the signals coming from individual individual neurons using different type of technique. such as mean field theory and have condensed our knowledge that we have from the Hodgkin- huxley equations using mean field statistics into population equations that are significantly lower, dimensional, which then. are the basis for the type of network nodes that we're looking at. Additionally, essentially, we're going from this type of action potential firings. This is a neuron number evolving over time. This is spike density that accompanies these signals to neural mass activity that we can describe in a closed fashion. Additionally, when talking about the virtual brain. Additionally, this is one of the key activities that we have built during the human brain project. Well, we we have built algorithms that allows us to build digital twins. Additionally, the virtual brain is a specific type of digital twin using neuroimaging data and individuals, neuroimaging data. Additionally, there are essentially 3 steps. Yeah, one, these are the network nodes number 2, we link these network nodes to network connectivity. There, since the nineties, we have diffusion, tensor weighted imaging. So again, we can go into the imaging signals of individuals. typically individual Dti that allows us to build the connectum. So the complete set of all connections between in our case individual brain areas. that allows us typically white matter fibers as you see them represented here when we co- register the network nodes on the one hand side coming from the MRI, together with a connectum in the same space we can build an avatar. So a geometric skeleton that allows us to be spent in physical space. This is actually very important. Yeah. Additionally, the numbers that we typically work with in the applications that we have. it's about 200 300 nodes. This is a number of brain regions. Today we are scaling it up to about 200,000 nodes. When we have 2, 300 nodes, a brain area is about 10 to 20 square centimeters. At 200 nodes we are entering into a domain where we can operate on the millimeter scale. This is actually the millimeter scale is important. When we are looking at other types of interventions, neurostimulation has been mentioned multiple times there we would be completely lost when we are operating on the low resolution scale. So this is one of the lessons learned during the human brain project. Additionally, you see some examples here. This is actually ex vivo representations of a connectome. This is from the big brain, where we use scans of Xv board that gets us on the Times on the spatial scale of about 2 300 micrometers. We have developed also techniques that allow us actually to make a merger between individual Dti, which is on the time scale on the spatial scale of millimeters, together with the ex vivo templates that allows us to increase the predictive power of the model significantly. Then the 3rd element is essentially putting it together the network and representing it in 3 dimensional physical space. Additionally, you see some representation here. So the geometry comes from the representation of the MRI on the one hand side. Then the topography comes topology. Sorry. The topology comes from the connectome, and we span it in 3 dimensional physical space. Additionally, what you see here when we connect it to the mathematics. we can. We use standard physics in order to map the source signals on the sensor signals. Here you see a representation. Eeg, but we can map it equally on the Eg. Meg or Fmri. The mathematics that we are dealing with. It's actually relevant for this talk. You see, it represented here, we have differential equations that are integrating over the connectivity information that we have available local dynamics and global dynamics which undergoes the time delay. The time delay is actually that makes the brain as a spatial temple system very unique, because you cannot describe it by the entire mathematical scenarios or toolboxes that we have, that we know from physics where we deal with partial differential equations, because this is actually in spatially variant. It matters where you are in the brain because the connectivity. So the interactions change. This changes much of the mathematics that we have to deal with. Yeah. So these 3 elements together defines the virtual brain. Additionally, then we have multiple ways of using it on the can perform straightforward simulations. On the other hand, we can use it as a template for inference. In which we are actually extracting information. That is. in the past 2 talks. You have heard the epileptogenic zone. Additionally, this is actually the digital twin loop that you see represented here. We from the real. the brain imaging data. We put them together in the way of in which I have just shown you. We equip it with mathematics. So going from avatar just pure geometry to a real functional digital twin. We can actually put it into inference context, where we can actually using Bayesian inference typically performing Monte Carlo techniques in which we sample the parameter spaces to estimate the epileptogenic zone. Once we do this, we have actually 2 levels of personalization. the imaging data that constrain the virtual brain twin second, the sampling, the inference that actually optimizes for this particular patient, and that allows us then, to do this type of simulations, as you see represented here, on the left hand side, the patient was virtualized. Additionally, then we can run simulations. These are simulation data. Where on the the blue areas represent the individual sources mapping on the seg electrodes and the seizure evolves spatial temporally across the sensors. These are simulated data for this particular patient. Additionally, we can go also onto since we are on the high resolution scale, we can also, for instance, extract the hippocampus, keep it here in the context. Additionally, here, you see, actually, the hippocampus simulations run that are evolving in very, very much detail, start developing, propagating waves within the hippocampus, and then the propagating wave front until the actually, the seizure stops. So we can operate on multiple scales a full brain scale. However, since we have the high resolution, we can also go into much detail here. Oh so the way we use it is as a causal hypothesis in the inference framework in which we are estimating heat maps of the epileptogenic zone pretty much along the lines of what Sri has shown you. Here. You have an example. often post surgical, MRI. The surgery has been performed here on the right hemisphere, and the heat map overlaid on the left hemisphere overlaid, coming from the estimations when you compare some of the performance thereof. Here you have clinical hypothesis. seizure free. not seizure free, and this is coming from the clinical estimation or the clinical hypothesis, and this came from the virtual brain, vp. Virtual, epileptic patient. You see that actually the precision drops down significantly for the virtual brain prediction for the not seizure free cases. Additionally, actually one of the key messages I wanted to share here with you. Why is that the case? Yeah. Additionally, where do we need help with regard to this? And why is that the case? Is the following bill explains to you how the positions for implantations are being chosen, used the history of the patient, and then, and estimation of the clinical hypothesis is being created based on the data that is available. Additionally, typically, you stay within the data space that you have accessible free works with her data within the data space that you have accessible. What we are doing is we're performing. We're taking an encephalomorphic approach. Additionally, we are actually modeling the totality of the entire brain and perform partial sampling, but infer. including including the connectivity, the entire brain as an inference space, and that allows us actually to make predictions about epileptogenic zones here represented in red that are actually outside of the accessible for data accessible space question. That is that an exotic case. Yeah, it's 1 of the questions you can ask, and the answer is actually well. 1st of all, let's look at the performance. Clinical hypothesis is the false discovery rate that is represented here. Seizure free, not seizure, free. When you look at this from the virtual brain twin for seizure, free patients, it's very low and it booms up. It jumps up for not seizure free patients. Additionally, what is behind. That is actually exactly what we just said. 29% of all the regions that are linked in the not seizure free cases that are actually outside of the accessible range. Additionally, this strongly correlates when you look at the overlap between the correspondence with the virtual brain prediction, it turns out that the majority of all the cases falls in the not seizure free cases. So what we are having here is an extension, an information extension. Taking the knowledge we have represented in the virtual brain, linking it to data and mathematics is nothing else than a formalization of our knowledge. We extend the information, we put it together, and we are able to make predictions in this particular space here. So we are running a clinical trial which has just finished. Actually, last year we wait for 12 months after surgery in order to be able to make a judgment about seizure freedom or not. Yeah. So this is, it has. This is the situation where we are, and patients are still being undergoing surgery. 356 patients have been included in the inter clinical trial. So this is the approach in terms of virtual brain. Can we go beyond that. It's just one application in just a few minutes. I wanted to share with you actually, how we can go beyond that and put it, for instance, in a context of neurostimulation. Since that has been addressed here, multiple times and neurostimulation can be performed either through non-invasive approaches using Eeg Tdcs. For instance, temporal interference is an upcoming technology or through implanted devices. Additionally, you can also stimulate with the seg that you have here. Yeah. So what we can do. and there it's absolutely necessary that we work with high resolution, virtual brains. So that allows us, for instance, to here you have again a representation of the hippocampus. This is the up amygdala. You can actually perform a forward mapping of the electric field that you use for the stimulation, and then actually compute in the case of the cortex or the hippocamp, in the context of the hippocampusy component. That is orthogonal that couples best with the brain tissue. Yeah, so when we do this, yeah. we can build virtual brains, using, for instance, interictal data, as Sri has shown you or we can actually use seizure data so interictal data to go through the virtualization process, but not stimulation data, how predictive is the virtual brain on an individual level. Because this is what we're after personalized medicine. Additionally, the, we can do that. Yeah. So we created virtual brains for individual patients in this case based on intericular data. Yeah, we did do it differently. Sri, we use intericular spikes, estimates, etc. So more traditional methods. Yeah and then we can go and stimulate the different seg contacts. Yeah, so here you have 3 examples. Additionally, when we do that in this simulation, we can actually simulate the stimulated responses of the system. Yeah of the brain system. Additionally, this is essentially what you see here. You have one particular. You have 3 different stimulation sites. This is the virtual brain data as measured in the seg electrodes. Remember, the patient's virtual brain has never seen stimulation data stimulating the 3 different sites and generating propagation patterns. Here no seizure has been triggered, and here a seizure has been triggered of type one and a different of type 2. So this is just one example that has been modeled. Additionally, then afterwards, in the patient, the same electrode context were actually stimulated. Additionally, of course I'm showing you a nice example. However, the bottom line is, I want to show you the spatial temporal pattern is one feature that we're interested in. Same thing you can do now with changing amplitude or frequency. So the stimulation parameters and this is one of the key challenges that we have in the clinic. How do we change the parameters in order to actually sample the activity of the brain. It takes lots of time, and it's a burden for the patient. Additionally, you see actually here again, that the performance for this example, that I chose works actually quite well, and we can do it systematically, which we have done for over 50 patients where we actually quantify the spatial temporal patterns, space and time. and can compute different types of metrics. Yeah, that are represented here. Additionally, essentially, it works very well. There is an surprisingly good predictive power on the individual level, on the. For in terms of spatial temporal dynamics that you have there in this 3 dimensional parameter space. So this links 2 different applications of the virtual brain on the context of this type of modeling. Additionally, I mentioned the neuromorphic activity or the neuromorphic activity we have done in the context of spinnaker and brain skills. We were not able to. We tried, but we were not able to use this type of architecture for this type of modeling. we have major challenges there. 1st of all, high resolution, we increase the resolution now by a factor of 1,000. It's necessary without high resolution. We cannot do any stimulation because it becomes trivial. Yeah. in term. I showed you some of the mathematics. Why. it's difficult. It's difficult, because we have time delays in there. We have noise in there. So it's a stochastic system. It's very high, dimensional, and we have very long stimulation times. We are in the real world. Fmri, resting state recording, for instance, is 20Â min. Yeah, it takes us about more than 2 days pure simulation time. If we want to do this type of simulation at high resolution, this is not something that scales up. We're doing simulations using Gpu architectures today. Yeah. However, it does not scale up, especially when we go to bigger patient numbers. Yeah, or in larger cohorts. Yeah. thank you. the other big bottleneck that we have is inference. Yeah. for personalization, we have to perform inference. Nowadays. The techniques we use is simulation based inference. Yeah, for this, we have to run thousands of simulations of these instances. For seg, for instance, we don't need 20Â min of simulations there. Tens of seconds is sufficient. However, times a factor of 1,000, we need help there. This is the type of inference we need the high resolution, as I told you, we cannot work without that. Thank you. Let me stop here. Some of my colleagues and friends have contributed to this that I display you. Thank you.

01:05:26 --> 01:07:26

**Grace Hwang:** Victor. So it sounds like you're presenting the computational advantages we're using neuromorphic approaches in your challenge slides. There is a long history in terms of neuromorphic architectures supporting simulations. On the one hand side. On the other hand, you saw, I put it in the context of brain stimulation. which is one of the discussion points that we have had here think of virtual brain and the need for neuromorphic architectures to help to perform the simulations. On the one hand side. On the other hand, to help to design better neuromorphic architectures in the use of stimulation, because you can. At least this is the hope I showed you the cases that work. However, the hope would be, can we use virtual brains as testing beds to optimize and improve your stimulation techniques using neuromorphic systems. So it was two fold the message. thank you for that. Thank you. Let me get these slides back up. We're about to go into the panel discussion portion, and if I could ask the panelists to come up as well as the presenters. if you're welcome to join the panel discussion up front. that's good. Okay, Ralph has spoken presenters Yes, please make sure your devices are muted, both the computer and the phone. so we're gonna I realize you're running a little late. We're gonna try to get you guys out by 12 0, 5, and what we hope to do during this panel, which will be moderated by Jessica. Additionally, I, we hope to do is to ask our panelists to introduce yourself. and we're going to this time. Start with Sid Cash. So, Sid.

01:07:32 --> 01:07:55

**Sydney Cash:** I'm not Bill Staley. I'm Sid cash. I'm an epileptologist and researcher at Mass General Hospital. Most of my research focuses on a lot of what you've heard about intracranial recordings and trying to understand the neural signatures underlying seizures so that we could build better devices to control them.

01:07:57 --> 01:08:19

**Nathan Crone:** I'm Nathan Crone. I'm a neurologist. I work at Johns Hopkins. Additionally, I also use intracranial Eeg to do research and functional brain mapping and brain machine interfaces. We've done some analyses of connectivity for epileptogenic networks. That's and I'll turn it over to Chris.

01:08:20 --> 01:09:00

**Grace Hwang:** We do have a virtual participant as well. If you could promote Giacomo Valley. However, in the meanwhile join us virtually. Let's go continue with with Dr. Kendall Lee, and we'll figure out how to. I'm actually going by my slides. Oh, so, Kendall, you're next. Kendall Lee: Do you want me to explain that slide or no, just introduce myself. Introduce yourself. Grace Hwang: But do them in like 2Â min.

01:09:00 --> 01:10:31

**Kendall Lee**: So my name is Kendall Lee. I'm a neurosurgeon at the Mayo clinic and the director of the neuroengineering and precision surgery laboratories. I've been given 2Â min for one slide. So when we think about neuromorphic and neurocontrol systems, I think that a lot of the field we've been focusing on the electrophysiologic feedback systems. So you know, you heard about that a lot. However, if we think about the brain, it really is electrochemical. Additionally, so our laboratory have been focusing on the chemical side. Additionally, so what you're looking at is a device that we have invented for the Maven which allows you to do. It's a multifunctional apparatus for voltametry, electrophysiology, and neuromodulation. Additionally, on the far right, you're seeing sort of high dimensional voltammetry. So these are newer techniques that we've invented we were one of the 1st when the brain initiative came out. This was through the brain initiative funding that can measure your dopamine serotonin. These things in the brain in vivo at the point of care. So within the brain itself. Additionally, what you're seeing here is how we're now using this technology for where we believe neuromodulation is going particularly drug addiction, psychiatric disorders. Additionally, when you start thinking about that whole other aspects of neuromorphic systems come into play which we can discuss.

01:10:32- - > 01:10:34

**Grace Hwang:** Great Chris, do you want to join us?

01:10:40 --> 01:12:10

**Chris Rozell:** Good morning. Nice to be here with you all. My name is Chris Roselle. I'm a neuroengineer and neuroscientist at the Georgia Institute of Technology lost my sense. That's fine. It's it's a very interesting for me to be here with all of you, because version 1.0 of Chris Roselle worked on neuromorphic systems. Additionally, I I met many of you in Telluride back, and I looked it up. Timmer. It was 2010 that we were all there together. Additionally, over the last decade, I've actually moved away from neuromorphics and toward clinical and translational neuroscience, neuroengineering. I work now in neuromodulation for psychiatric disorders. So deep brain stimulation or treatment, resistant depression especially. Additionally, we build electrophysiological biomarkers of the recovery of the brain under dbs. So I'm very interested. Yeah, there's the side. I'm very interested in notions of how we can put advanced processing, including, as I think, Tim Dennison alluded to this morning. Not just artificial intelligence, but explainable artificial intelligence systems on board chips for longitudinal monitoring, because something like depression is very different from epilepsy, from movement disorders where you have something episodic. You're trying to address right now. It's a slow disease with a slow time course and a slow recovery. So there are a lot of uses for monitoring both the brain and the body longitudinally over weeks and months. As the system is very plastic that don't have anything to do with feedback control and closed loop systems. Actually so very interested for a discussion of how neuromorphics can play into this.

01:12:11--> 01:12:14

**Grace Hwang:** Thank you, Chris and Giacomo, if you can just unmute. I believe you can introduce yourself.

01:12:15 - - > 01:13:31

**Giacomo Valle:** Yes, sure. Sure. Do you hear me? Yes. Okay. Okay. Great great. Yeah. Hi, everyone. I'm Giacomo Valle. I'm an assistant Professor Chalmers, University of Technology in Gottenberg, Sweden. I'm a neural engineer. However, working in the field of brain computer interface and aeroprosthetics to restore sensory motor functions in people with spinal cord, injury, amputation. and hand impairments in general, we want to use a neuromorphic approach that in our field is sometimes called like biomimetic. However, we are trying to understand if these 2 pathways are at the end. The same thing where? Replicating how the natural system is encoding the information. we can leverage this our neuroscientific understanding to encode better our artificial sensation, and so at the end communicate with the nervous system in a more realistic and effective way.

01:13:33 --> 01:13:41

**Grace Hwang:** Thank you, Giacomo. So I'm gonna note. Turn over to Jessica to kick off us. Kick us off the 1st question.

01:13:42 - - > 01:14:10

**Jessica Falcone:** So we have just some guiding questions. The 1st is more clinically focused. So just skipping how you would do this. However, if you had a low power, implantable chip that could run any algorithm of your choice. Real time, closed loop AI machine learning, what would you use it for? And then kind of the subtext of that is, what are the encoding and decoding challenges that we're facing in nervous ordered or nervous system disorders.

01:14:12 - - > 01:14:13

**Grace Hwang:** So who wants to start first?

01:14:15 --> 01:15:15

**Chris Rozell:** Okay, I would. Yeah, I would start by improving the devices that we currently have. Bill did a great job. You know, outlining the limitations of the current devices that we have for epilepsy. We'd have more channels. We'd have better sampling. We'd have a greater signal to noise. We'd and hopefully we'd be able to do a lot of the computing in a fully implantable Wireless device. That would, you know. take advantage of all the dynamical systems approaches that the tree and and Victor have taken and put all that into something that the patient really doesn't have to think about, really. Additionally, so that's a big, tall task that probably won't be reality for another decade or more. However, anyways, yeah, I'll let.

01:15:19 --> 01:18:26

**Kendall Lee**: Can I answer that as well. So in at Mayo clinic. One of the things that we are focusing on is the neurochemical sensing as we talked about. However, one of the challenges we're facing is as we are recording this data. The amount of data is just is huge. Additionally, then, as we think about closed loop systems. I think a little bit similar to what John Boyd once said here. John Boyd was a colonel who thought deeply about closed loop systems what it means, and he kind of narrowed it down to 4 things what he called uda loop. you know, observation. orientation, decision, and action. Additionally, each of these steps. You know, there's a lot we can talk about which I think the neuromorphic systems of the future are going to have a very important part in it, because I think we're pretty good. Now at looking at some of the observation stuff, electrophysiologic, chemical, these type of things. However, as you're collecting data now, you really have to orient yourself and to me. That's where neuromorphic systems could play a huge role in the future low power lot of information, you know, analysis very quickly. and then, as well as in the decision side, you know, the action side is just the Dbs electrode, or whatever you're going to put into the into the brain. However, the decision, too, I think, is going to be really important. Where, when I look at where artificial intelligence and deep learning has come. We've been very good at collecting a lot of information, processing a lot of information, but within it is wisdom, and I think that you know, since the whole word of neuromorphic, you've got to ask, why do we want to go neuromorphic? Well, in terms of the deep learning systems? We are at a technology where the computer scientists have, you know, analyzed how we look at information, how the human brain looks at information and follow sort of the Huber and weasel model of vision systems. Additionally, you know, we go from v, 1, v. 2, and so forth. However, there's also feedback loop systems within that. Additionally, you know, Grace, you and IA little bit talked about this couple couple of days ago that the current systems of artificial intelligence really are operating on the neuroscience of like 60 years ago. and where I think the neuroscience of today is going can really have a huge impact on where neuromorphic systems of the future are going to be our work. We went from Parkinson's disease tremor to attacking psychiatric disorders, and this is a whole nother beast altogether. As you mentioned that we're going from motion to emotion. Additionally, as we're now playing with emotional circuits, I think that it's going to be very important that we think about how we use the future of neuromodulation interface it, you know, with with the brain. Additionally, as we're doing that, I think that in my opinion it would have to be neuromorphic, meaning that we have to infuse into it those things that the brain's doing and then figure out how we're going to control depression, control, drug addiction, these type of things

01:18:29 - - > 01:18:31

**Grace Hwang:** jumping in order of magnitude and complexity. Any other thoughts on this question before we move on

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**panelist:** just a very just a very quick thought, the way you phrased it. How would you use it? 1st thing I would like to look into is if I can get more than one chip. However, multiple chips. After all, the brain is a spatial temporal system. I don't want to be limited to one particular location from my experience, modulation and manipulation. When you have access to multiple sites significantly. Easier questions of routine, ethical authorization, etc, will come up, of course. In this particular context, however. it's easier to manipulate a network when you take the network character into account. So that should be definitely one of the strategies we would have in mind when exploring this type of novel technology.

01:19:31 --> 01:20:27

**Panelist:** of a quicker comment. Quicker So it's a warning. So you look at your phones. Engineers used to be clever with how we managed power and computational power on phones, and as and computers, and as the cpus got more and more powerful people stopped thinking and just said, Oh, we can just brute force this through. Additionally, saying, Oh, we're just make a bigger chip, and we're just gonna throw it at it, and and we lose track of of our cleverness. Additionally, I think that would be a big problem, especially in this situation, where we have no idea what we're looking for or what to do. Additionally, so just making a bigger and nastier hammer when we haven't figured out the input or the output of a closed loop device is going to be fraught with peril.

01:20:30 --> 01:20:37

**Grace Hwang:** Do you think there's any advantages in using onboard systems to learn about the fundamental principles of our of the problem we're trying to solve.

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**Panelist:** What I'm talking about is is the problem of we've never had enough time to train and optimize. and having something on board, would perhaps allow us to optimize. I'm sure that at Medtronic they would have loved to optimize their stimulation. It's just not something that's very possible. Additionally, in every one of these situations that would be the best. We haven't had a model system. Virtual brain is a great way to do that, because you can start optimizing. However, taking the next step into optimizing in vivo is tricky, but would be possible with that.

01:21:18 - - > 01:22:19

**Panelist:** Let me interrupt and ask you what you mean by optimization. Because we're, you know, we're talking about one of the big problems that I see in the world of neuromodulation and epilepsy, and particularly in neuropsychiatric diseases, is the timescale is not great in the sense that. Additionally, maybe you're talking about optimization of different ways. However, you know, to know whether let's just take Rns as an example to know if it's working. I wait usually 2 to 3 months to see whether my last change in stimulation has any impact on the overall seizure rate of the patient. I've got 0 other biomarkers I could use, besides the patient telling me, yes, I'm having seizures or not over a fairly long time scale. so that just from a time point of view is a hard system to optimize. Additionally, I think it's even worse in neuropsychiatric diseases for various reasons. So I think one of the things we need from these kinds of chips. Additionally, these approaches is other ways to think about the disease that doesn't rely necessarily on a single large biomarker like a seizure. For example, for us to be able to optimize them so we can have a rapid, more rapid time course of changing things. I don't know if you'll always be able to. So, at least in some cases in our hands, with treatment, resistant depression. Time is an ingredient in the therapy.

01:22:19 --> 01:23:15

**Panelist:** right? We see unpublished. However, I'll share with you. Here we see white matter restructuring. We see change in the white matter, pathways that appear to be a part of the stabilization of the recovery in the patient, so it may not be possible to have shorter time. Scale observation, biology, I mean, biology wins in these situations all the time, and the biology might not be. It's the same way with rns and epilepsy. I think there's more and more data that what the device is doing. unlike what is intended to do isn't just stopping a seizure, or maybe most of the time isn't actually stopping a seizure at all. However, it's leading to some sort of network change. Additionally, that network change takes time. However, wouldn't it be nice to know on Day 2 that you're heading in the right direction? And now you just got to wait versus Nope. Wrong stimulation. Switch it up so that you can get in the right direction. We got nothing that does that at this point in time that I know of.

01:23:30 --> 01:25:17

**Panelist:** I'll say, maybe to get back to your original question, at least in the case of psychiatric disorders. We are, you know, a generation at least behind and understanding the electrophysiology of these conditions compared to movement disorders and epilepsy? Right? And so it's actually a very difficult question to answer, because I don't know what I would do if you gave me some magical neuromorphic chip that could compute anything I wanted. I actually have no idea what I would do with it right now. even in the Dbs world. There, what order of magnitude! Half a million Parkinson's and movement disorder patients with Dbs implanted right now, I think, globally for treatment, resistant depression. That order is something more. On the order of 200 to 250 patients. and only a small handful of them with recording devices. So it's actually very interesting. I loved, of course, Tim's talk this morning, but seeing the progression of the Medtronic devices, from the activa to the summit to the percept. we actually, we see a device where the rough edges of the initial prototypes are getting smoothed out, and you get to something that's commercially applicable. However, in some ways they're actually more restricted devices. right? They're not able to observe in as open and unconstrained of a way as the early prototypes could, because, of course, they're targeting their commercial market of Parkinson's disease. So the percept the commercial device is really very geared toward what they know they can sell and make money on, but it actually makes it more difficult to do the kind of free form observation in the real world over long periods of time that we need for psychiatric disorders. So again, I don't know that my biggest barrier is not having a magical, neuromorphic chip. It's maybe the commercial and regulatory sort of constraints that would actually prevent a company from building such a thing. even if it wasn't neuromorphic, but that would allow the sort of observation that we need prior to knowing what it was going to be useful for and what the indication was going to be that could be revenue generating.

01:25:17 --> 01:26:09

**Panelist:** Yeah, I would just like to agree and also get back to my original point is that until we have devices that can capture more than just 4 channels of Eeg. We really don't know what we're missing and until we can implant those for a year or 2 or or more. We really don't. There's just a lot of data we just are not working on right now. So then I think we may find neuromorphic chip would be very helpful with that. However, until we have that data, I think we're really very data poor right now, even though we seem to be swimming in data with with the what we've got so far with 4 channels, I mean, that is, that turns out to be a lot of data if if you can, if you can get all that data. However, we still really lack information. To to make the kind of decisions and that you're talking about

01:26:10 - - > 01:26:19

**Grace Hwang:** sounds like you're advocating for the status quo from a clinical perspective, and that you can learn everything you need with your existing approaches as long as you have data.

01:26:20 - - > 01:27:27

**Panelist:** No, I'm not at all advocating for the status quo. Yeah, the exact opposite of that I think we really need to push forward with the devices, with many more channels than we have right now. I mean one of the things just to underline this very practical situation we face all the time in the epilepsy clinic is that you know, epilepsy is not due to a single focus very rarely unless it's in the hippocampus. It's not a single focus. Okay, it's a network. There's an epileptogenic network. Additionally, then we're seeing this very often when there's a lesion, and then we put stereo, eg. Electrodes in the lesion, but we also put them in the hippocampus. We find there's seizures coming from the hippocampus as well. There's secondary epileptogenesis. These patients are coming to us after they've had epilepsy for 10 or 20 years, and the disorder is not limited to a single lesion or focus. Additionally, so we really need to be able to sample that entire network or parts of that network, at least in order to develop effective therapies.

01:27:30 --> 01:28:38

**Sri Sarma:** Can I comment? So I. So it's really interesting. So you're hearing, like the need for sensors, better access to information and not enough data. Additionally, then, you know, intelligence so forth. However, I think I want to emphasize, I think, what's really important, what Bill said and to what Sid was saying is, even though we have AI, and maybe we have neuromorphic computing. Let's say we had all of this. I still think we need to make room for scientific discovery. AI is not going to solve everything. Additionally, so here's a really clear example. What Sid pointed out, which is he? Does, you know they do surgery on one of their patients, and they have to wait 6 months, you know, an epilepsy patient to say, Okay, did your seizures reduce in frequency. Right? So we don't even have a biomarker of brain health. In fact, Victor and I had a conversation many, many months ago of things that we're trying to pursue in others as well, which is what is a healthy brain? How do I know that when you've done a resection, or you treat that this brain is not going to ever cease again, or very unlikely to cease again. Right? That's science, that's discovery. Additionally, what I want to emphasize is regardless of all this, we have to still be open to that.

01:28:46 --> 01:28:49

**Grace Hwang**: We have a question. Feel free to come up to the microphone and ask your questions so that people in Zoom can hear.

01:28:50 --> 01:30:03

**Robert Stevens:** Good afternoon, Robert Stevens, Johns Hopkins University. So I'd like to congratulate the speakers for their remarkable talks, and the panel members for their insightful comments. So I want to sort of step briefly outside of the realm of pathology, seizures movement, disorders, psychiatric disturbances, and talk more generally about the question of intelligence. Additionally, so this is a question, maybe initially for Dr. Jersa. However, perhaps other panel members would like to comment. So, Dr. Jersa, am I pronouncing this correctly? I'm sorry. so maybe you can teach me afterwards how to. However, anyway, so that it. Really, this question is about Agi Asi, right? So it's obviously fast forward to, you know, 2,024 in the future. However, you're talking about a virtual brain. Right? I was wondering whether you could comment on how we could. Potentially, you know, leverage this virtual brain as a method to achieve human level machine intelligence, and maybe even super intelligence. You know. So setting aside pathology, but thinking more in general terms about achieving this this general intelligence that we all possess, but that machines don't seem to possess. Do you think the human brain project has contributed to that? And do you think your own work is leading in that direction.

01:30:05 --> 01:32:28

**Viktor Jirsa:** Thank you for the question, actually. what you have seen today, I focused on epilepsy. Yeah and I have shown you a successful approach to brain activity, modeling brain activity. spatial temporally. I have not made a single statement about thought, cognitive function, etc. They're the question of representation comes in today, the virtual brain sleep. It can go through anesthesia. it can age, it can become epileptic. So there are with the same model we can systematically, under correct parameterization or parameter changes. We can describe the brain states and also mimic individuals. With regard to this. we cannot do more today we cannot do more. Is there capacity for steps beyond that? Going into the direction, as you have? Asked Agi, for instance. This question comes up, my with several colleagues, we are discussing these possibilities. We are looking at Llms. How they can actually be mapped on the connectum if the connectum. Its topology can be supportive of some of the processing. It's very exploratory today. Yeah, at the moment, I can make only statements about brain activity and most promising steps forward are the chemical level, by the way, fast and slow systems, neuromodulations. Which introduces another dimension helpful to go into this particular direction, helpful to look into medications, but also helpful in modulating of activity. To start building a library of potential dynamic states. When I say states, it's always dynamic. So we can start developing the repertoire and the toolboxes to start posing these types of questions. This is where we are. I don't dare to go any step beyond that.

01:32:30 --> 01:32:40

**Panelist:** Maybe I think this is a really important question. As we go into neuromorphics, you know, you use the word intelligence, you know. Another word, perhaps is.

01:32:54 - - > 01:32:57

**Grace Hwang:** And maybe I shouldn't use the word consciousness. which is okay. So we are over and we are over. So James has been standing patiently for a long time. Do you have a quick question?

01:32:57 --> 01:33:22

**James Cotton:** My question was just it. It seemed like there was an apparent bit of a contradiction, right? I heard a lot of people saying the need for technologies to record more richer data in the real world. At the same time we heard earlier that it's like 12Â TB of data. We can collect data near unlimited things with depth mapping. Can you resolve that contradiction like, why do we not have the data that we need?

01:33:24 - - > 01:33:31

**Panelist:** so big difference? The terabytes of data was inpatient with specialized equipment and the ambulatory devices are extremely limited.

01:33:33 --> 01:33:37

**Audience-James:** But can we not get the insights when people are in those situations about?

01:33:35 - - > 01:34:18

**Panelist:** I mean, the brain is still a very artificial situation agree. However, if we don't get insights from that, will we really get insights from more complex data in the real world? So yeah, there are lots of people doing the inpatient, cognitive testing. They've been doing this for quite a long time. It's tricky, but it's limited. Additionally, the biggest problem is that these are epilepsy patients that are trying to have seizures. Additionally, so you're doing memory testing or whatever type of cognitive testing on people that have just been hit by a truck, basically, and who have baseline problems to begin with. Additionally, then they maybe had a seizure. Additionally, so lots of lots of issues going on. However, they do that again. It gets sorry it gets back to that time issue.

01:34:24 --> 01:34:31

**Panelist:** These are diseases of long time periods, and we're getting a snapshot of a snapshot of a snapshot.

01:34:32 --> 01:35:11

**Panelist:** just to give a very, very concrete example. So the use of dbs, like stimulation for treatment. Resistant depression has a long and kind of winding history. Over a few decades they had looked at acute onset of stimulation in interoperative recordings basically before there were ambulatory devices that could record. Additionally, the acute electrophysiological response is actually in the exact opposite direction of what's needed for stable recovery. Longitudinally, if we would have built a closed loop system based on the interoperative data, we actually would have flipped the sign and we would have been looking for exactly the opposite of what we needed to look for, that we only discovered with longitudinal monitoring.

01:35:12 - - > 01:35:15

**Grace Hwang:** So This needs to be our very last question. I'm so sorry.

01:35:17 - - > 01:35:59

**Audience:** Let me just. We'll ask it. I'll take this into lunch. It's because it's more maybe too philosophical for quick. However, for lunch conversation, and especially I see David McMullen in the back. So that my concern about neuromorphic approaches is that we want to use these to treat brain disorders if we truly made it neuromorphic, like a brain. How do we ensure that the algorithms we created don't have their own disorders? So we create roselle disorder. Yeah, we keep the Sid cache maladaptive right off the bat. So don't do that. So that's the one where those of you with experience. I'd be very interested in. How do we prevent it? If we truly go, nor neuromorphic, we don't actually create new diseases for our patients.

01:36:09 --> 01:36:11

**Grace Hwang:** All right. Thanks. I think this is. Sorry, Sid. Ralph, do you want to?

01:36:13 - - > 1:36:34

**Ralph Etienne-Cummings:** So there is one in the afternoon we'll have another hour. Meet this around right? So it'll be the 2 sessions coming together. and we'll have opportunities, you know, because the discussion here has been primarily focused by the by the panelists, but I'd like to get the audience.

01:36:36 --> 01:36:39

**Grace Hwang:** So let's thank our speakers and panelists one last time and enjoy lunch.