NeurOnAir Podcast

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Transcript of Episode 4

A glimpse into the Neural Code: Theoretical Neuroscience

Guest: Larry F. Abbott, Ph.D.
Hosts: Şeydanur Tıkır & Oren Weiss

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Şeydanur Tıkır: Picture a neuroscientist in your mind, doing experiments to understand how the brain works. Did you picture this lab with a pipette, a brain, or a model animal? For some neuroscientists, none of these are in the scene when they explore the brain. It's rather a scene with computers and equations. In today's episode, we will explore the field of theoretical neuroscience, which uses mathematical and computational techniques to understand the brain.

Our guest is Dr. Larry Abbott, a pioneer in the field of theoretical neuroscience and also a co-director of the center of theoretical neuroscience at Columbia University. You're listening to NeurOnAir, a podcast made by students and postdocs at Albert Einstein College of Medicine in New york. Don't forget to follow us on social media and visit our website at neuronair.org

Şeydanur Tıkır: Welcome to NeurOnAir. It's our pleasure to host Dr. Larry Abbott in this episode who is actually invited to give a talk at our neuroscience department today. And he also kindly accepted to be our guest for our podcast. We are your hosts today, two graduate students from Albert Einstein College of Medicine.

Oren Weiss: I'm Oren Weiss.

Şeydanur Tıkır: I'm Şeydanur Tıkır

Oren Weiss: Dr. Abbott, thank you for sitting down with us to talk about your research.

Larry Abbott: Sure, yeah. Thanks for having me.

Oren Weiss: So just to begin, what would you say the main motivating questions are behind your research?

Larry Abbott: Yeah, I think I just like to figure out how things work. You know, when I was a kid, whenever my parents bought a new appliance or anything, I always took it apart. And then I was always terrified whether I could get it back together again. You know, I've just always kind of wondered how things work. And this is a fantastic system to wonder about that. So I think the underlying motivation is just that, tinkering with things and trying to figure out how they work.

Şeydanur Tıkır: I think it's amazing to see how this innate curiosity could lead to amazing discoveries in science. So before diving into specific questions, it will be helpful to learn about the field in general. Can you please define the field of theoretical neuroscience for people who are outside of this field?

Larry Abbott: Yeah, sure. Absolutely. So you know what we bring is mathematical analysis, computer simulation, those tools to the study of neuroscience. Obviously, neural circuits are incredibly complicated and that's an important tool, not to say, of course, all the experimental tools important tools are important tools too, but this one is an essential one in this particular system because it's so complicated. And so most of us, I certainly do work very closely with experimentalists, not just, you know, dump the data on me and expect me to run some models, but really the whole process, thinking about the experiments, thinking about which directions to go, you know, we're another kind of specialist in the game to help get to the answer.

Şeydanur Tıkır: And I was wondering based on your personal experience in the field, how do you think the role of theory in the broader neuroscience community has changed over the years?

Larry Abbott: That's a great question. I think it's changed a huge amount over my time in the field. You know, actually, the talk I'm going to give today kind of has a nice example of that. So when I first started in the 90s, I think the role of theory was to throw out ideas to explore what can networks do, how could they compute, and how they store memories, you know, all that kind of stuff. But it was sort of on the speculative front and kind of to, you know, lead to new ideas, drive people's imagination, and, you know, inspire experimentalists. But of course, there’s been such a revolution in techniques. My talk today is going to show kind of all of them, the genetic stuff, the connectomics stuff, the incredible imaging people can do, the manipulations... It really changes so suddenly it's, it's like, well, we got to get this right, now. You know, how does it really work. And actually in my talk, a lot of the examples of really clever ideas in the 90s that were more speculative, you can really see now where some of them are really implemented and you see exactly how they're implemented. And I think that's exactly how theory should work. You know, throw out an idea, it may take 20 years for you to figure out the validity of it, but some of those ideas will be very powerful. And then, of course, we're in the stage now, as I say, getting it right. Of course, the general ideas are right but the implementation is much more specific to a particular animal or circuit.

Oren Weiss: So you said before that in the 90s, a lot of what theoretical neuroscientists were doing was just throwing ideas out there and now we're more in a phase of confirming. So this is related to the next question. There's a common criticism with Theoretical neuroscientists that theorists are postdicting, which is designing models to match empirical observations rather than predicting new behaviors from theoretical principles. In an article, called Theoretical Neuroscience Rising, you present a good opinion about this and you talk about how this is somewhat ahistorical in science, in general. I think you gave the example of quantum theory, how that was a postdiction of the ultraviolet catastrophe, in a sense. And you note that the true value of any model is how it generalizes to other systems - and provides valuable new ways of thinking, rather than predicting new behavior. So I was wondering if you had any example from your own research of a model you helped develop that will offer a new way of thinking about neuroscience while postdicting rather than predicting?

Larry Abbott: Let me say one thing about that. That was a Neuron article about, I don't know, quite a few years ago by now, right?

Oren Weiss: Yeah.

Larry Abbott: And actually Neuron recently contacted me and said, you know, maybe you want to update that article.. and I said, yeah, I really do because so much has changed. One thing that’s changed is, there are more predictive models now. I mean, I was just mentioning about models in the 90s that turned out to be right, you know, so that's changed in a way, but, you know, it used to be: well, predict something in a way that's the ultimate test. And you know, if you did many great theories in physics, including general relativity and all that, it would fail that test. Actually, it predicted the bending of light, but it was based on the precession of mercury, for example, and that was known, It was after the fact. So I think it was a bad criterion. Anyway, in my own work, I will mention old work since that you know that was sort of an old review. We did some stuff on synaptic depression and its role in adaptation. So adaptation was a known phenomenon, you know, we didn't predict anything new. But I think we gave people new ideas about where it's coming from, where the mechanism is from. And I think because neuroscience is so much about the mechanism, that's why you know this sort of postdiction is not bad. You can say, well, I knew this phenomenon occurred, but I had no idea why. And of course, back in those days when I wrote that review, you couldn't do the manipulations you can do now, you know. You now can say I think you know this cell type is really important in this phenomenon fine you know will silence that cell type or activate that cell type that wasn't possible back then. So, I would say the game has also changed in that regard.

Şeydanur Tıkır: I actually liked what you wrote over there a lot. I think it provided me a better perspective. You know earlier I was thinking that if a model just replicated something that we observe in the brain, I was considering it less compared to the models that can predict something new. But I like the view that you provide in the paper because it changes my focus to thinking whether it improved the way I think in science, rather than just using binary rigid criteria such as postdicting versus predicting.

Larry Abbott: You know, for me, both judging my own stuff, but also if I read a paper, I just want to know, has it given me a new insight into how this thing works. And, you know, even if it's not completely right the idea. Sometimes I say, you know that's a better way for me to think about this circuit or this mechanism. You know, it's kind of in the eye of the beholder that way though.

Şeydanur Tıkır: So most of these studies that you did are coming from beautiful collaborations right. You're a very good collaborator and good collaborations usually lead to very creative findings. I think the dynamic clamp technique that you developed with Dr. Eve Marder et al. could be a good example here. I actually did my Masters's in a lab that used the dynamic clamp and it was so amazing to see this powerful method at the beginning of my basic neuroscience training and to be able to manipulate and simulate neural activity in real-time. I was so impressed. Regarding these collaborations between experimentalists and terrorists, what are some common barriers to forming good collaborations in your opinion, and how can we overcome these barriers?

Larry Abbott: Yeah, you know, I've been incredibly lucky throughout my whole time in neuroscience that I've just had amazing collaborators. And, you know, as a theorist that's essential. I was just going to talk about the dynamic clamp a bit and then you ask the question, you know, that was a perfect example where Eve [Marder] and I came from very different fields, we talked for about a year before we had made any sense to each other. She was willing to put in that time and I guess I was willing to put in that time. And one day we just went to lunch and I sort of came at these things from the equations and she came in and knew about actually putting electrodes into cells, and we just said “hey, we can build this thing”. So what you see is collaborate with a good experimentalist but you've got to find somebody you can talk to. So what I always tell my students is to really look for that. Somebody could be an absolutely fabulous experimentalist, a fabulous person even, but if I feel like I just can't communicate on a very intense level, and just say, second of work, there is nothing wrong with the person, there is nothing wrong with me, it's just not going to work. So, you know, I think it's a very interpersonal relationship. It's like making a friend, that you don't really know what clicks, but sometimes it clicks. So I would say don't underestimate the interpersonal part of it, not just being a great scientist, doing great experiments, of course, that's important, but I look for people that just have a kind of really good communication with.

Şeydanur Tıkır: That's very interesting. So you're saying that it actually happened very spontaneously right. You two were just having lunch one day and then came up with the idea. I think it's a very good example and hearing this example also makes me think about the importance of environments, in addition to interpersonal skills. I think there is a big role of academic institutions to create environments that can help collaborations across different fields. Actually, I just remember that last year in the summer I was traveling in the Netherlands. I visited a university there, and I saw that students don't have their offices shared with their lab mates. They are rather matched with students from different labs in their offices. They mix students in on purpose, to encourage them to get together, discover different fields, and extend their horizons. And maybe this is very important, right, because it encourages people to get together in a very casual way just like in the example you gave.

Larry Abbott: I agree with you entirely. In fact, you know, in COVID, sometimes people say “well you theorists are lucky we don't do experiments”. So we can, yeah. And we can work that it's fine that way. But we don't do what you just said: we don't bump into somebody in the hallway or in the elevator and say “Hey, what are you working on” and you know often the greatest stuff comes from that. So my advice to a theory graduate student or some just talk to people, you know, every time you bump into one here coast student say “hey, have you discovered anything, what’s new”. A lot can happen that way and we try to make a very open-door policy here, for example, sometimes either postdocs or students when they're evaluating data, they'll actually move over to our theory center and take a desk and then there among all the postdocs and students, you know, they can ask, they can exchange ideas. So yeah, I completely agree with you. I think the layout of space is really important and you know my advice is: take the time to go sit next to somebody at lunch that you don't really know and see what they are doing.

Oren Weiss: Yeah. So these past couple of questions we've been talking a lot about, I guess, I don't want to say conflict or tension between theorists and experimentalists but I think that’s certainly there. And something I was interested in, since you've been in theoretical neuroscience for about 30 years, and you've seen this explosion and the increased relevance of theoretical neuroscience in neuroscience as a whole. I was wondering, what do you think the greatest contributions of theoretical science have been to our understanding of neuroscience in the brain and as a whole.

Larry Abbott: Yeah. I think the basic point sounds trivial, but the mathematics behind it is not so much. It is really an ability to think about collections of neurons, populations of neurons doing your calculation. You know if anybody looks at a brain is going to say, obviously, that one neuron doing the work. But building the techniques that allow you to see, you know, this is a very high-dimensional system. None of us are good at envisioning high-dimensional systems. And so working out the mathematics of that, figuring out where your intuition, in higher dimensions your intuition can often be terribly wrong because we don't picture it that way. And so I would say the greatest contribution that I can see is really that, the tools for thinking about high dimensional systems and mapping from recordings onto population vectors and state-space representations. That caught on very fast. I give it experimentalists a lot of credit for this because I think at first, people were like“wait a minute, just tell me about spikes and rates, don't tell me about this state space and vectors”. But they got it a lot, you know, most of them. You know I think it's the language of circuits now, that's a big advance.

Şeydanur Tıkır: Having talked about circuits and these tools and systems that let us explore the circuits. When I look at the model systems that you work on, I see that you pick various model systems that have very well-organized circuits such as the mushroom body in the fly olfactory system and cerebellum. They all consist of these beautiful parallel structures, right? So you obviously pick the most well-organized circuits that exist in the world. Can you maybe explain to us the key features of these circuits that allow you to make powerful discoveries?

Larry Abbott: Yeah. So I'll give you the true answer and then I'll give you the sort of long answer. The true answer is that I'm really good at picking collaborators, you know, and they pick the animals. So honestly that's the way I work. So if I've arrived at beautiful systems is through beautiful collaborators, but anyway. So this is something about theoretical neuroscience that we haven't gotten to. If you're a lab you pick an organism, it might be a mouse might be a fly, and that's what you do. And so as a result, sometimes that can be parallel lines, you know, in progress in neuroscience. And I think one of the big jobs of the theoretician is to cross over and say “hey you know there's something cool discovered in a fly maybe, there's some idea of that you comply to a mouse”. I think it's almost an obligation for us to move cross-species because the rest of the field can't do that. You can't close down your mouse lab and open a fly lab next week. So I've tried to do that. And I've tried to cross-fertilize the ideas as much as possible. And you know, I kind of enjoyed it at all levels. Another thing people make mistakes in theory, sort of, there's one theory that you would apply for everything from humans to, you know, C elegans that's not true. You know, you would tailor the techniques to the level of the study of the organism and you're going to use different techniques to understand a person, than you're going to do to understand fly.

Şeydanur Tıkır: So you certainly see a value in moving cross-species. You also move between animals and machines, and study the principles of the brain and learning in both artificial and biological networks in your research. And you also care about making artificial neurons more relatable to biological ones. And I have two questions about this. So first, is it possible to make artificial networks resembling biological ones. And the second question is whether this is a desirable goal. Do we really care about them resembling each other? I guess the second question is also related to this idea of interpretability in computational neuroscience. So for example, we have these ultra-fast deep networks performing black-box type analysis. They're not really interoperable, because we don't know how they're doing what they're doing. However, the question is: Does that really matter? Because they are capable of doing things in a way that is comparable to humans. So what are the reasons for still looking at other network models that are understandable?

Larry Abbott: Yeah okay, let me extend because this is sort of an extension of what we were just talking about, that you don't necessarily apply the same techniques to all systems. So, you know, today I'm going to talk about a fly circuit. I think it would be a little crazy to tell you to apply machine learning to that circuit. it's a small number of neurons, we can identify them. It wouldn't be the appropriate level. On the other hand, you know, if you're talking about the primate visual system. I think it would be equally crazy to try to figure out what every neuron and that system is doing, it's just not the right level of description. And so I think once you accept multiple levels of description, you kind of get over this. t Well, we're going to replace that we don't understand the primary visual system with the fact that we don't understand this network that does object recognition or whatever. But you know that's a fantastic achievement. The fact that we have machines that can get to human-level on stuff is amazing. To me, I think that on occasion, the machine learning people get an idea from neuroscience that will happen. I don't think they're going to end up with Machine Learning devices that look, you know, just like brains, there's no point in doing that, but they'll get ideas. And for us, I think it's just an incredible tool. I'm a big fan of that tool for one reason that you mentioned, which is, it allows you to test ideas at a very high level. It used to be, you know, if I had an idea of, oh, here's the new kind of synaptic plasticity, maybe it does x. I would try it in such a simple model that it wouldn't be really challenged. But, now I could try it on some machine learning system that does human-level tasks and say, does it do anything? You know, it's a much more rigorous test. So my approach to machine learning is to take that basic framework but stick in biological elements and say, what do they do in this context of a very rich complicated system. You know, it's in the early days, but I think that marriage is going to be really, really something, very very good.

Oren Weiss: So, for example, for convolutional neural networks like the topic for condition. The fact that if you add random noise to an input image and it completely ruins the object output the labeling, that's not necessarily something that concerns you?

Larry Abbott: Sure, yeah. Sure it concerns me. You know it concerns you. It's sort of interesting to tell you the truth that maybe you know you can be a human being, without really being a human being, you know. That these systems can identify objects is pretty much as well as you are. But they may be doing it by a very different system. And I think those adversarial examples point that out, that they may be using a different system. You know having n=2 is better than n=1, if we have two systems that are able to do this complicated thing I'm, you know, figure out how they're different. Figure out how one's better than the other. You know yeah yes I do worry about those things. But I'm more excited about the possibilities.

Oren Weiss: Right, and especially with spiking networks, which I, which is what you've been working on recently.

Larry Abbott: So spikes are just a nightmare. You know, honestly, if you want to know the most amazing thing about our brains is, you know, of course, they can do amazing things, is that we do it with spikes. It's such a terrible way to run a brain in my opinion. So that's a huge challenge. You know, if you listen to my talk today, it's not spiking models, you know, we can achieve a whole lot more without going to spike models. Every time you go to spike models, you know, you get all of these sorts of technical details. Technical problems because just spikes are just an ordinary way to run a network. I would love it if somebody would make or breakthrough there and build a more robust spiking network. So you could just flip it over very easily. That's not true yet. So there's a mystery I would say at the biophysical level and it really. In the fly circuits, I'm talking about it's almost more severe because they're not very many neurons. You know, I think the standard answer but spikes are all we got so many neurons because of so many synapses. You know it all just adds up. Even that is not so easy to get it to work. But in a small animal with not that many neurons. They probably do all sorts of tricks at the biophysics level that we are not completely on to yet, for smoothing out the spikes. If you wanted to know, you know, what's the Bugaboo, it's spikes in theory.

Oren Weiss: Um, so, somewhat related to that last question. You've been publishing recently about connectomics. Recently co-authored a paper with a whole bunch of offers about the mind of the mouse, users have connectomics in mice. And in that same “theoretical neuroscience rising” article before you mentioned that in analogy was artificial neural networks connectomes may not tell you what a network does, but it may provide some other useful insight such, it was constructed. So what are the ways for making the best use out of high-resolution data that we've obtained in neuroscience that we are hoping to obtain? And how would you use goal-driven machine learning to inform us about data?

Larry Abbott: Okay, yeah. So, the connectome. It's interesting. I didn't even remember that I said anything about connectome in that old article. You know, the reason I got involved in it is because I realized when it was, you know, obvious that the fly connectome was coming out. I had no idea what to do with it as a modeler. Certainly, I'm not going to build a model with every connection in there. And I would say, you know when I wrote that earlier thing I didn't have any idea and it really shows you sometimes you just dump the data on the table, then you figure it out. The connectome on the fly changes everything. And again, I mean, you know, you'll see that in my talk that being able to look at that level of detail is just completely amazing but in ways, you didn't expect. And let me give you one example from the fly. Something totally unpredictable. So, in flies, you cannot look, at least the classical anatomist, if they looked at an E.M. picture of a synapse, they couldn't tell the transmitter type they couldn’t tell whether there was a GABA synapse or a glutaminergic synapse. And that was a big limitation because it meant when you got to connect them there was a connection but you wouldn't know whether it was excitatory or inhibitory, so that was considered a big minus. But When these E.M. images started coming out, there was a huge amount of data group at Janelia led by Jan Funke applied a machine-learning algorithm to a ton of data and built a system that can tell the transmitter. You know, it just looks at synapses and tells you what. It seems to work really pretty well. So, um, so, you know, when you get a ton of data, you don't know what's going to happen. I would never predict that I don't think anyone would ever predict what would happen. And yet, there it is. So at all sorts of different levels. And, you know, machine learning, I think what we can do, for example, is look at the statistics of connections and match them up. You know the fairest answer is “I don't know”, it's early days in that thing. But, I've seen that essentially every discussion about fly circuits refers to connectome them now that I ever have when anybody. So it just seems like an amazing new opening of a new door.

Şeydanur Tıkır: I think that an example of using machine learning to extract the neurotransmitter information from connectomics was a very good one. You know when I look at the history of these discoveries, such as connectomics or transcriptomics, I see that first, there is a big excitement phase where we were so passionate about trying to obtain the full connectome or full genome of species. But then once we do it, there is a phase of uncertainty where we have no idea or little idea what to do with it. But, in the next phase, we actually start finding ways to extract really useful information with the application of machine learning and other computational methods. And who knows what else we will discover in the future. As you are saying, they are getting more and more useful over time. So we talked about connectomics and networks. But you are also interested in how these networks and connections switch their behaviors, right? They start responding to a stimulus that they haven’t been responding to before. They switch to a new way of functioning. When you wrote a chapter for the book called 23 problems in neuroscience, you picked that topic of switching for your chapter. And the name of the chapter was “where are the switches on this thing?”, which I really like by the way. As you were mentioning over there, there are huge gaps in our knowledge of switches in biological brains. Although we know about some potential ways for biasing network activity in the brain such as gain modulation, inhibition, as you listed in the chapter, there are still critical gaps. So it's been 15 years since you contributed to this book. And I wanted to ask if you still think that this is still one of the most critical issues in neuroscience research today. And how far do you think we are from achieving the goal of discovering the mechanisms for switching in the brain?

Larry Abbott: It's great to bring that up because I think it shows you when progress occurs in science, often it isn't that you answer the old questions, you just realized there were the wrong questions, you know.

Şeydanur Tıkır: Yeah this is the natural process.

Larry Abbott: Yeah, yeah, you know, and I think we have tons of examples in physics of that where you know it isn't that you answered it. I would say this is one of those. I don't know the answer to that question. But if I was going to write that article today I think I would say it differently. What more looks like. And as, again, as you see, a larger broader range of neural activity in brains is that that kind of everything is sitting on top of everything. It isn't that you switch. And a really good example of that is that it really looks like, it's true in the fly brain is true in the mouse brain, you know. If an animal's running the entire brain is affected by that action. It seems completely nuts. And I think in those days that was said, well, how do you switch so that running doesn't affect you knowing some part of the brain that doesn't care about running well that doesn't look like that's what's happening. This is, again, has to do, earlier I talked about, you know, the mathematics of populations, I think. Nowadays, what people would say is there is kind of orthogonal directions. So I can have one signal going this way and one signal and going this way and they won't interfere with each other. That's kind of a linear view. But I think it's the It's probably better. So I was thinking, well, you just turn this one off and you listen to this one. But, if they're orthogonal, you can accomplish the same thing in a more population way. So I think now, I would ask that question by how do you arrange all these signals, not to interfere with each other, even though they're simultaneously there. And in the linear picture, you would say "I just make them orthogonal" but we need to do a little better than that because it's not a linear system and in a nonlinear system, you know, you can't be orthogonal, but they'll be rotated. So, that's a really cool example, I'm glad you brought it up, of the fact that the question has changed. Maybe we still don't have the answer, but, I think we have a better framing of the question.

Şeydanur Tıkır: You were also pointing out an important future direction which is expanding our understanding of neural circuits from the representation of information to cognitive processing. Do you think that the lack of knowledge on switching or this omnipresence is a current bottleneck in achieving this goal?

Larry Abbott: Yeah, yeah, I think so. This omnipresence, you know, of these kinds of running signals all that it's very mysterious right to me. This idea of many kinds of information are sitting on top of each other, I think it's a real puzzle. And from that, we picked out the relevant stuff and hopefully do the relevant action. Yeah, I think that's a major question and cognition. And again, this is one where machine learning might be able to help us. One thing is Machine Learning tends to be, commercially you build it for a particular task. One of the things that I think will help in a biological sense is when people build more general-purpose machine learning that not only does the task but identifies you know the thing I'm supposed to do now is to talk to you I'm not supposed to, you know, dance or something. How do you decide what the appropriate task is for a particular moment? And then we're going to see this problem because you're going to take everything in from that have decided "Oh I'm supposed to talk now", or "I'm supposed to get up and run out of the room now" or whatever.

Oren Weiss: Yeah, it's been before you're talking about how it seems like all these processes sit onto each other in an orthogonal way. I was wondering how it does that, or how does that relate to this topic because it's receiving a lot of attention in neuroscience recently which is dimensionality or low dimensionality of neural signals, and how we can kind of combine all these things without interfering even though the brain seems to communicate in a low dimensional space.

Larry Abbott: Yeah, yeah. Now you know there's a bias there because low dimensional stuff is this stuff we're going to be able to understand first. And I think you know we've been seeing the low dimensional examples and I think that's fine because you want to start working out in a what that is not too complicated. But I suspect you know if you're out in the world and you know here in New York dodging the traffic and talking to somebody and waving. You know, it's pretty high dimensional there's all these tons of stuff, as you said, sitting on top of each other. You know, that's where this idea of selecting maybe rather than switching is really going to come out in a big way. But obviously, you want to study it from the ground up. You don't want to start with a hugely complicated situation.

Oren Weiss: Right. So for our last two questions, we're gonna move to something a bit more general. What do you think is an area of neuroscience that has been, under-explored and would benefit from attention for theoretical neuroscience scientists? I feel like a lot of theoretical neuroscience research is focused on the same page centers on visual systems. And so I was wondering, what do you think would be an area that would benefit from more theoretical attention.

Larry Abbott: Yeah, yeah. Another great question. Let me just tell a little joke or whatever that you know. I sometimes imagine there's some incredibly great genius mathematician, you know, who doesn't know any biology. And sits there. I will make this she. And works it out and comes out of the office, they look, I got it. You know, I have a system. It's just like a brain and can do all these things. And then you tell this poor woman. Well, but the brain builds itself. You know, you have even gotten off the ground, yet. So my answer is development. It's something that most theoretical neuroscience completely ignores we just say there's the brain. It's God knows how I got here, but there it is. And I have to figure out how it works. And you know, that's a hard enough problem. That's what I do. I don't work in development, I don't know a whole lot about development, but it seems to me we got a whole other problem is that the stink builds itself and So that to me is, is an underdeveloped area if I can use the same word of theoretical neuroscience that would be cool to work on and you know it's not like they don't cross talk because a lot of times if you're trying to say why is a circuit like it is. Well, a lot of is because that's a had to be built that way. And we may be arguing over this is optimal for this. That's optimal for that when reality, it's just that, in order to get these accents to grow in the right direction. You know, you had to do it that way. So I think theoretical neuroscience would be stronger if we really had a developmental component in the theory.

Oren Weiss: So, when you say development, you mean like morphologically like how the neurons come to be at particular places.

Larry Abbott: Wires up And you know what the constraints are that it has to, not only do you have to build the right circuit, but you have to find the right neuron and you know these incredible constraints there to be able to build this thing from nothing.

Oren Weiss: Yeah, it's very interesting. I was trying to understand if that's true if that's somewhat related to learning how these circuits.

Larry Abbott: Yeah, well. So I think it's a great question how related, is it to learning. I don't know. You know, maybe it's a lot of the same mechanisms. Certainly, I would say the work in developments that **can Miller** has done in the way in the past. And then recently, he's been doing it again is kind of linking it to the same ideas as learning. But we don't really know. You know how much is it, you know, targeting through various targeting molecules. That, that, that's why you somebody needs to do this, since more about the development.

Şeydanur Tıkır: Along these lines, let's say that you study the fly brain and find out some learning rules that led to the development of that network. Do you think that these rules that you discovered can apply to other species as well? In other words, do you think that there's a general code called that we can crack?

Larry Abbott: Yeah, my guess. I don't know, but my guess is yes because it's such a basic problem. How do you wire up the nervous system that you know when evolution finds us a solution tends to find it. And, not either it can be because evolution passed it on to both let's say mammals and flies, or it can be parallel evolution. And I think, you know, in the olfactory system which you talked about machine bodies part of that factory system. There's an incredible parallel between flies and mammals that is not you know inherited from a common ancestor. They just, they just evolved the same system because it's the right way to build an old factory system. So I think that's an amazing example where you could easily say local fly in a mammal. There's nothing to do with each other, and yet the systems, you know, have a real one-to-one map practically between them.

Oren Weiss: Yeah. and there is a recent paper that you published called evolving the olfactory system. Just to explain in that paper you describe. You build an artificial neural network with the biological constraints and ou you show that it matches the whole package system to the fly. So do you view that lineage is an interesting direction to go

Larry Abbott: that's a whole other issue, which is evolution. You know that I could have answered I put it on development because but you know the other thing is, of course, how did these things evolve. And you know what, we're taking advantage of their in machine learning, you know, you call it learning, but you're really building a system. Let's say that does object recognition or whatever. You're really not replaying learning. You're replaying evolution, right, you're, you're saying, how did we develop a system that's so well adapted to do our vision. We're taking advantage of that we're saying “let's replay evolution from a machine learning standpoint”. I think that's a whole other area, you know, ultimately When we get an answer in biology. It's also always comes then. Okay, but how did it evolve, okay, this is how it works. But how on earth did it possibly evolve this clever system that's always going to be the fundamental question and we're gonna have to think about that too.

Şeydanur Tıkır: That is such a beautiful question. Actually, that was the first question that I investigated as a grad student. We were asking this question of how neural networks evolved by comparing evolutionarily related sea slug species at multiple levels, at the network level, single-cell level, behavioral level, and transcriptomics level. I think it was an amazing system to explore how the circuits have evolved. Yet as I continued my training, I realized that the question was much harder than I imagined. I think it’s a very difficult question.

Larry Abbott: And, you know, as we know more about the circuits, we can get at this. I'm thinking of Vanessa Ruta who's a Rockefeller who has really done beautiful work on different species of rusafa law and why they, become they want to meet with each other and not with other species, which is a whole species. Species, whatever, how they become species. But anyway, and it's, in their sensing of the pheromones, how do they evolve to prefer a different pheromone or send out a different pheromone and identify mates of their own species And she's beautiful work on figuring out how the circuits have evolved in order to, to, develop these preferences and mating preferences.

Şeydanur Tıkır: Sounds very interesting I will check it out. Before closing, I want to ask one last question that might be helpful for trainees and students. For a beginner student who's interested in theoretical neuroscience, what are the most important skills that you would advise them to develop? And I know that some students particularly have that question of whether it's more important to have skills in programming and simulations, or in biology and neuroscience. Maybe you can touch on that a little bit too.

Larry Abbott: Yeah, sure. Let me just start by saying something that sounds completely trite but it's incredibly true, which is, you know, follow your heart. I think students synthetic and I ought to do this. Add to do this. Do what excites you, because you're going to be best at that and, you know, so let me just say thatobviously, you want to develop as many skills as you can. I would only say that it's harder to develop math skills later than it is in biology. So I was 40 years old when I switched from being a physicist to a neuroscientist. And, you know, it's easier to switch in that direction. Let me just put it that way. When you say this. Everybody thinks you're an arrogant physicist, you think you know physics harder. It's not the physics is harder instead physics is weirder in a way, you know, it's such a specialized talent. I often like to compare it to saying, you know, Somebody wanted to become a novelist, they could do it at any point in their life and you know maybe they'd be a great novelist. But if somebody wants to be a concert violinist, forget it. You know, if I told you something. I'm going to be the conscious right one is, you know, I'm never going to do it. Because that you got to do it. Young and I think math is kind of this strange talent like playing the violin that you gotta do young so I would just say do it in the right order. And then, you know, do what excites you.

Şeydanur Tıkır: That makes a lot of sense to me. Start from the weirder one if you are going to learn both fields eventually, right. But more importantly, follow your heart and passion as you were saying in the beginning and it looks like that was what you did and you ended up where you are at now.

Dr. Abbott, it was a pleasure talking to you today. Thank you so much again for being our guest. I will see you later in the day at your seminar at Albert Einstein College of Medicine.

Larry Abbott: Okay, thank you. Thank you both. Yeah.

Oren Weiss: Thank you. We know you have a very busy day today.

Larry Abbott: A lot of people

Oren Weiss: Yeah.

Larry Abbott: I'll see you later in the day.

Şeydanur Tıkır (Episode summary):

Your hosts for this episode were Seydanur and Oren. We enjoyed learning about theoretical neuroscience as it relates to the broader neuroscience community from Dr. Abbott through our discussion of so many thought-provoking ideas. Models can offer new ways of thinking about neuroscience, as Dr. Abbott so wonderfully embodies through his collaborations with experimentalists. A perfect example is his contribution to the development of the dynamic clamp method, which was a shared effort. Just as our brain must integrate the processes of all of its regions to create your unique thoughts, we must talk to scientists from other subfields to create an enriching environment that will lead to creative tools and solutions.

So where does the field go from here given its recent advancements? When we asked Dr. Abbott's opinion about what area is still underdeveloped in the field, his answer was ironically brain development. It's something that most theoretical neuroscientists completely ignore, yet, understanding how the brain constructs itself could have repercussions in many other subfields, from learning to organoids, to disease mechanisms. These are some of today's critical issues in neuroscience that theory could help solve, including one more enigma Dr. Abbott added: the omnipresence of signals, and how these signals are arranged in the brain without interfering with each other, even though they're simultaneously there.

Experimentalists and theorists often exist in separate scientific circles, but we hope that our interview with Dr. Abbott can help stir up the imagination of scientists in both worlds to bring them together to help explore new frontiers in our understanding of human biology's biggest remaining mystery.

Thanks for joining us today! Visit our website neuronair.org for more resources about today's episode and our guest Dr. Larry Abbott. You can also follow us on social media @neuronaircast to leave comments on today's episode or to get in touch with us directly, email us at neuronairpodcast@gmail.com. And finally, if you enjoyed the episode, please subscribe, and review us! See you next time!

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