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Combination of experimental and theoretical approaches to move the field forward – a moderated summary discussion

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Abstract. Discussion moderated by the authors on the topic of “Combination of experimental and theoretical approaches to move the field forward”. This is the summary discussion at the 14th International Mechanics of Hearing Workshop held at Helsingør, Denmark, 24-29 July 2022. This paper provides an edited version of the recorded videos of that session.

DISCUSSION SESSION

Bastian Epp: It's a tradition at Mechanics of Hearing (MOH) that there is a longer discussion at the very end to kind of reflect a little bit back what happened. And if there is anything that you want to bring up. Where does the field go? What are the critical points that we should address? And it's a little bit like the 101 sessions. There are no limits and there is nothing stupid. Let's just bring up these comments. This is like really a documentation and a timestamp of where the field is right now.

Laurel Carney: I thought it was incredibly useful to see so many optical coherence tomography (OCT) type presentations. As somebody who's seen them before, but I always have trouble digesting them and really understanding them. So I thought that the tutorial session on that was incredibly helpful. As well as seeing all the presentations and then Brian's presentation this morning discussing this rotation issue seemed incredibly important. So anyway, that's just an appreciation, I guess.

Wei Dong: I want to add something. I think [this] is a very successful conference. The conference covered from basic and fundamental research to the translational research and extended application in the clinic, which led to the development of new hearing devices and improvement of clinical diagnoses and treatments. In addition, Laurel's talk is very impressive. It raised the question for researchers focused on cochlear mechanics to re-consider what the main feature for us is to investigate as the major cochlear role for human speech perception and sound perception. And also, the talk from Dick raised the question on how to improve the collaboration from the experimental part to the modeler part. The combination of the experimental observation and theoretical approaches will further our understanding [of] underlying mechanisms and move the field forward in parallel. It is more than welcome for the modelers to give us feedback and guidance for future experiments.

Steven Neely: Okay. So my comment in response to Dick's presentation. I don't think we're ready for a standard model yet. And part of the reason is the computational difficulty. We're orders of magnitude away from being able to have a nonlinear time domain model of the entire cochlea and sufficient detail to reproduce all known experiments. So I think we're stuck with multiple models for the foreseeable future.

Dick Lyon: Yeah. Thanks, Steve. I got a similar comment from several other people and I don't disagree. But the extreme alternative is what I see too much of which is that everyone makes a unique model for their own experimental data. We need more convergence than that. And obviously we're not going to have one standard model. But if we can have a few models that get more comprehensive over more data domains, that's going to be helpful.

Dáibhid Ó Maoiléidigh: So can I just make a quick comment about this because I have a very different opinion as to what the problem is. I don't think the problem is that we don't have enough computational power, and I don't think the problem is we don't have enough data. I think we have a problem that the system we're looking at is a complex system, and by that, I mean, it is thousands – however you want to parametrize it - number of variables and parameters. And I don't think reproduction of all the experimental data alone will lead to us understanding the cochlea.

So I would like to ask any of those who have used their model to reproduce data: Do you feel like when your model has reproduced the dataset that you now completely understand your model? I will point out, for example, the Mammano and Nobili model has been presented repeatedly here and we would all agree it's a very good model. But yet we keep on reanalyzing it. So it reproduced the data. But it seems to me that we're still trying to understand that model and what it can do.

Lisa Olson: So one of the things I liked best about this conference was Renata's talk, which she called a tutorial. But I think it was just a very nice description of the importance for 3D models, what they can give you and ways to think about what the fluid mechanics is doing without any activity by itself and how that adds to the function of the cochlea.

Bastian Epp: I can also probably add on the model part. I would probably even put it further. I think it might also be worth thinking about metrics we are using. Diek Duijhuys has been saying that for a long time. A transfer function or an impedance doesn't make sense for a nonlinear system. And if you go to these computations and these are limitations, a lot of it happens. What caught my attention the last couple of years was that Fourier transform is just a description. It doesn't tell you anything about the mechanism. It's just a description of what you see. And it's just one description. It excludes a lot of mechanisms about energy transfer from one frequency to the other which could be an integral function of part of cochlear function. But it's completely gone once you kind of projected on an orthonormal axis.

So I think and this goes into it in the direction of nonlinear dynamics. We don't really have these metrics which we can just pull out of the head and say this is a description everybody understands. And I think this might also be one of the clues that we might go to of going more nonlinear and actually also questioning the metrics that we're using.

Karl Grosh: So the obvious question goes back to the first question that was from MOH 101, which was when you use one, two and three dimension models and how to model complexity. I think sometimes it depends on what you're looking at. Sometimes the 1D model is what you need, right? So we know it's incorrect in how it represents the fluid, but it tells you about some mechanisms and can instruct you about different wave propagation mechanisms.

When you go to a 3D model like Mammano and Nobili and others, you do get to the point where you've actually been doing a numerical experiment. And the beauty of that is that sometimes you are making predictions about responses like the reticular lamina that no one had data for, right? And then you can go back and check those predictions truly as a prediction. Because you're not fitting for that. And of course, you probably have to go back in and reclose it. So that I think that Dick's goal is a good one. And I agree with Steve that that the complexity in the time domain aspect of things is really hard, right? And we have challenges there. But I think it is a good direction to go, which is to try to build some models and have people play with them. And people who can play with them - maybe it's sort of like us - you know, experimentalists and others. But it also might be some numericist hiding out somewhere in a computational

maths department who says ‘Wow, you guys are really not doing this as efficiently as possible’. And that would be beautiful, too.

We'd love to see that. I think it is something we can start to think about now. And I remember we were in Portland, I think, and Domenica Karavitaki said ‘Why don't you computational guys put your model on the web? And I also remember my thought was, oh my God, I could never. I mean, it's just too much, right? But now maybe we can start to think about it, I think, and move towards that. Not to say that any one modeler we put our model up and we think it's the best. I mean, of course we do because we're working on it. But you know, I mean, we realize there's holes in it. So it serves as a direction.

Dick Lyon: So there are a lot of models on the web, and that's been useful for people that are comparing them. But I want to just comment quickly. You talked about the complexity of the cochlea and as models or as Dáibhid mentioned. So you talked about how it's complicated. And he said it's a complex system. That's one of the things I address in my book. Is that complex or is it merely complicated?

Because I think there's an important distinction. And I think it's merely complicated. Which means we'll be able to understand its behavior from the behavior of its parts eventually. Whereas in a complex system like the brain, you probably can't do that.

Karl Grosh: So if I said it's complicated, right? It can be reduced to its components. Yeah, I agree. Whatever I said, that's what I meant.

Dáibhid Ó Maoiléidigh: I'd like to advocate for - learning when a model does not reproduce data. There is a good example that I taught recently. There is this old paper from Jim Hudspeth from 1977 where he proposes that the channels in the hair bundle are directly, mechanically activated. And in the paper, he shows that the activation can be understood - the activation of currents can be understood with direct mechanical activation. But he also shows that the closing of the channels is not explained by the model. The model completely fails to explain the closing of the channels. And the fact that the model failed led them to conclude that there was something they were missing and led everybody to go searching for that missing thing, which became adaptation. So by missing something, they learnt what was up, you know, they learnt something. And I think that's a great example. It's great to push that model to the limit where it breaks and then you learn something. And then they had to come up with another model to fill the gap.

Tony Gummer: I just like to make a comment about Dáibhid's and your comment, Karl, about the Mammano and Nobili model. For me, that's a fantastic model. Sometimes I have the impression that we're just analyzing the model. But what Alec and also Vaclav have shown in the last few years is that this model can produce a lot of information because it's not just a numerical model. Alec has developed analytical solutions for various conditions. And I've really learnt a fantastic amount from that model.

Christopher Bergevin: I'm hoping that Bastian and Wei will do a little analysis to count the number of times the word model was said during the session. And I think it means very different things to different people. I also like Dick that dodged the question when I asked him that earlier after his talk.

But I think kind of roughly what we're talking about here is how does the mammalian cochlea work? And I just want to make one mention from a broader comparative view. There's not really any such thing as the mammalian cochlea. There's all different sorts of ears we can talk about gerbils and chinchillas and mice and differences there. But that's different from, say, the human cochlea, as Heidi was talking about or something like a bats. There's just different sorts of things and that all ties back to the word model. So I would just stress we should try and be a little bit more careful with what we mean when we're using the word model, because otherwise we're just going to be kind of keep having the same conversation over and over again.

Samiya Alkhairy: So I wanted to follow up on Dáibhid's point. I certainly agree that a discussion of limitations is quite important. And on the other side, I think a discussion of assumptions is also equally important. Which I think

sometimes we neglect to do. Tying it in or extrapolating to non-model sort of things. I think discussing things that might seem inconsistent with experimental data conclusions are also something that would be nice to discuss as opposed to just one perspective.

Robert Raphael: I think it is as physics versus biology. In physics, it's just we're going to get the grand unified theory explaining all the phenomena. And in biology, because the system [is] so complex - what I tell my students is you want a model that's useful. And one of the main criteria to tell me is just what you were saying: motivating the next experiment. So say about the model. You have the framework for interpreting data that you wouldn't have if you were just doing the biological experimentation. You motivate the next experiment, you predict; you fail and then becomes an iterative process.

Now on the complexity point, what you said reminded me I think it was in 1999 Mechanics of Hearing meeting. Maybe it was 2002. Jülicher and Duke first came up with the Hopf bifurcation in hair bundle, proposing it for the mammalian cochlea. And George Zweig was there, and he just really [weighed?] them over the coals for this. Because what he said was whatever nonlinearities are present in this system - a system as complex as the mammalian cochlea - [I shouldn't be saying mammalian cochlea? I apologise, Chris. What term would you like me to use?] His point was that it's never going to reduce to something so simple as a Hopf bifurcation. You will never be able to replicate this in any simple mathematical formalism. And I figured you'd have an answer to that, but I just wanted to quote George Zweig.

Lisa Olson: OK, so just to get away from Hopf bifurcation. I'd like to get back to the experimental side of it a little bit because we were all excited about OCT. But I think to some extent, we don't really know quite what to make of those measurements yet. Thinking about Heidi's animations where it looks like the cells of the organ of Corti really are just like bags of fluid sloshing around in that passive prep. It's really such an open time right now experimentally to try and understand. We have fortunately, I'd say that a lot of what we already knew experimentally about the enhancement of the peak or the emergence of the peak in the healthy cochlea especially in the basal and middle cochlea is not being turned totally on its head by OCT. It isn't like, Oh God, we have to throw all that stuff out. But it's more the measurements from inside the organ of Corti are helping us to understand how that motion comes about. But I think so far we haven't gotten that new wisdom. We just are getting all these pieces. But it's really exciting times in experimental work to try to make sense of the findings.

Dáibhid Ó Maoiléidigh: So I'd like to comment on the utility of models, and I think your point to bring up is really important. It's really important to build the model to answer the question that you're interested in. And as modelers, we have a tendency to tell our experimental colleagues we do it because it's simple. And they think, oh, you're just lazy, you're just not going to work hard enough or we do it this way because we want to have a toy to play with. And they think, oh, this is important. This isn't just fun. You know, you should be doing something or we talk about realism versus not realism. None of these things are really quantified scientific approaches. These are just things we say. Whereas what we should be saying, in my opinion, is: I'm doing what I'm doing because I think it's the right approach to answer that question. And if you have a specific problem with the approach, then we can discuss what the problem is with the approach.

What my feeling is that a simple approach will work. A lot of the time for central systems, right? A lot of the models are input output relationships. Nobody would suggest you need to model every neuron to understand the brain stem. But you may want to model every neuron if you want to understand one box in the brain stem. So it's just choosing the model appropriately.

Melia Bonomo: I just wanted to add something to the discussion about models as well. When thinking about making a useful model, often we might not need to really reproduce every single thing we see in experiments, right? And think more about what's actually useful to the system itself. So something that struck me was during Laurel's talk, where she said that when she started recording in the midbrain, it changed her view of the peripheral auditory system and how the brain really cares about these fluctuations [and] doesn't care about the average rates of the fibers. So I feel like thinking about within the system what information is being used at each step and using that also to drive than what we actually want to reproduce, right?

It might not be useful to really reproduce every single little thing we see, but more like what's the system using to get the information from the external world to our brain? Something to consider.

John Guinan: I also want to say something about what you what you consider as a model. So the talk I presented, I would not have said that I had a model. I had a sort of a conceptual framework for thinking about a problem that was different than the previous conceptual framework. And so I think that what I'm arguing for is that a model doesn't always have to be in the form of a mathematical model for it to be a useful thing. It can be something vaguer, like a conceptual framework that points out a different way of looking at things that needs to be substantiated both experimentally and with more complex or more definitive models. So I think there's a lot of different ways in which you can approach things, and models don't always have to be a mathematical model.

Christopher Bergevin: Just a quick follow up to John's point, I would say it's a word I think all of us know, but it's probably not one that we use all that commonly and maybe we should, rather than use the word model all the time, maybe some sort of heuristic. Because I think that's kind of what you were also alluding to. It's kind of a framework for ideas that can then be formulated into something that's a model that can be used for predictive and descriptive.

Robert Raphael: Just to add to that conceptual framework. They are great. But you also have testable and refutable experimental predictions, and often people forget about the refutable. [It's] a high criterion, really. So something you can actually test and quantitatively measure and then experiment will get the wrong answer.

Dáibhid Ó Maoiléidigh: Can I quickly ask about the refutation. If somebody presents you with a model and a prediction and the prediction turns out to be wrong, that you tested it. In this audience, the experimental community.: Do you now consider that model to be a failure and of no use? And if that person continues to make predictions which turn out to be wrong, do you now think I can't trust that person because they keep producing predictions which are wrong and there's something wrong with their modelling approach? Because it's possible that the modelling community don't want to make wrong predictions, right? Because you don't get labelled as the person, but inevitably some of your predictions are going to be wrong. I think you can learn something from that, but I'm just wondering about perception.

Sonal Prasad: Dáibhid and Karl have raised really, really good points, and I think we should, definitely. I'm an experimentalist, and if I'm modelling, I [have] a prediction or something and it fails. For me, that's the right way to go. It has to fail. And maybe we should really bring in some computational people, as Karl said, that the way they do things and like a programmer, they just don't make a program, a complete program and then test it to the end is going to fail. They do like step by step, you need testing. And as I see the whole cochlea of the inner ear, you cannot make a model for the whole organ. It is going to be highly complex. So you have to test like a unit, by unit, you need [bases] like one frame, like, just the outer hair cell, then the inner hair cell and then test that. And maybe you don't call it model, but you need testing and that has to fail. Then it tells you that yes, you have to find limitations and you're reaching the potential and you are going in the right direction. The testing doesn't need to pass. It doesn't. It shouldn't pass. If it's passing, then you're doing something wrong. And then at the end, as he said, like then you make a comprehensive model towards then by passing like testing each and every sort of unit of the cochlea.

David Slater: I'm just wondering being sort of new to this community. If it doesn't already exist, when somebody publishes a model, should there be an explanation of how they think the model could be verified. Even if the verification or validation is not something they could do themselves? Just as a thought.

Marcel van der Heijden: A brief follow up on David's comment. In order for other people to test someone's model, it would be helpful to actually publish online not necessarily the code, but a working version online so that other people can run the model independent of it. Because, yeah, I've talked to several models here and they agree, and it's a lot of work. But that would be very helpful [to] just throw it out in the wild and in for other people to test it against their own data or their own ideas. That would be very helpful. I think in some other disciplines, it might already be the standard, but here it's certainly not. It would be very helpful.

Laurel Carny: Yeah, I agree, and that reminds me, I forgot to mention that our models are all online and, in the cloud, now. But somebody I think they gave us credit for that comparative model this morning. But we don't our group doesn't have any credit for it. But Peter Majak with the AM toolbox is actually somebody who is really championing sharing models. And not only the code, but the exact code that was used to make figures. And that's really true. So there is a lot of emphasis, I think, on that. That's happening.

But to get back to your question, to be honest, I think when you do see a model, it gives wrong predictions. I think it's first of all, important to figure out why. But once you do understand why and realize that this cannot make good predictions, then I think it's fair not to trust that model. Maybe not the model. But, you know, sometimes you have to move on from models. And, you know, we've all had bad models in our past, but it is this it's hard to follow up and advertise that.

So that gets to your point. It is probably worthwhile when we make new versions of our models to also explain why what was wrong with the last one that made us change it and make it more clear how things progress, because it's probably not always obvious to anyone outside of the developer. Along with ways to test it, which is a really good suggestion.

Eric LePage: Yeah, I'd like to make a general comment that the crew has changed a bit since the first meeting. We don't have the people who have evolution as their major outlook in this group. We're all phenomenological and dominated by the sense of precision. Science has got to be precise, and we don't have the Geoff Mandley's here and the people who give us an outlook, what we're dealing with 200 billion years of evolution. And the notion is that whatever we do, however, we decide that the system has evolved. It must be within our mind, within our models of how that could happen. We don't seem to be allowing for the possibility that somebody could come up with a simple description, which would be an overall simplification. It's got to be precise. It's got to be whatever. Somebody once said, was it Einstein, if you can't explain what you're trying to do to a seven year old, you're missing the point - that you're not getting the simplicity, the simplicity of outlook. And so my question is, to what extent could we be mangling the data in the way we think about processing it? And what I presented was the notion that the cochlea could have come up with a totally different solution to the problem. The evolutionary process. And it looks very, very different. But what I tried to suggest is that our standard method of processing data in the expectation of our model about it must be a very small vibration in some way. If we are actually processing the data so that it's mangled, we could be introducing massive complexity, which doesn't exist.

Karolina Charaziak: I have a more general comment, and also I really want to get you to catch the cube for the last time. In general, I think that the comment made about sometimes models not being correct. I think it's important to show that also in regard to the data we do experiments that sometimes just don't work. And as someone that relatively junior. I can't even count how many times I get excited about something at the conference, and I talk to someone that's been in the field for longer. It's like, Oh yeah, we've done it 20 years ago. Doesn't work. Great! I'm just going to repeat that then. So I don't know what the solution to the problem other than to talk to other people. But I think negative results or sharing what didn't work and why you think they didn't work, or even if you don't know why it didn't work, just vocalizing it. I think it's important to just keep moving forward and not running in spirals or circles.

Bastian Epp: Spirals are good!

Karolina Charaziak: Yeah. Depends if they go up or down.

John Guinan: So we've been talking a whole lot about models. I suggested another topic that might be talked about is: What would you like to see done experimentally? And that could be motivated by your model of something. But what would you like to see experimentally?

I would like to see more optical measurements that take into account and really figure out how much is radial motion, how much is longitudinal motion, how much is transverse motion? So that's my wish list.

Christopher Bergevin: Five syllables: Lizard OCT.

Samiya Alkhairy: OCT measurements as a function of frequency and also as a function of location. And if I may add one additional thing, having something like an AMT where people upload their models and model codes to something like that for data, I think would be quite useful. A data repository.

Marcel van der Heijden: Yeah, to address that system in a primitive way: Share the data behind a published figure, downloadable and I mean, it's a small community and you can just email and get more data. I think the answer to that question is also has to try to stay a community and be in touch with people willing to share.

Samiya Alkhairy: But sometimes, you know, people lose their data or, you know, it's in a very old format and sometimes people's grad students or people leave the field.

Marcel van der Heijden: About directionality of motion. Multiple groups, including ours are working on that and you can expect multiple approaches that try to address this question. So I think that this is in full focus of current work, OCT work.

Bastian Epp: I think in general, one could summarise this data management might be a good thing to do. Given all that, we have storage space and all that, but that's that costs a lot of time. That's the problem with our incentives regarding publications. Nobody pays you for having like a really nice repository with documented data and everything. But it might be something in a good dialogue to actually to work on. I mean, this would be super constructive in the end.

Dáibhid Ó Maoiléidigh: It's not so much necessarily this community, but maybe some of you work on mice, mouse mutants or what age of animal. Being young gerbil is great, but is it different from slightly older gerbil? And I don't know. Cochlear location as well as you can specify, mid base apex is very non-specific. So if you have any knowledge of the specific location, you can use one of the auditory nerve fiber maps to get some idea. It's super helpful for the modelers to constrain so that we're not trying to not mix parameters as much as possible. So. That's what I advocate for.

Steven Neely: I have a suggestion for an experimental measure that I would like to see. The experimental measures that I've been involved in personally were mostly all with human subjects. And one set of data for human subjects that I haven't yet seen reproduced in the laboratory animals are on tuning curves obtained by suppressing distortion product otoacoustic acoustic emissions. But we have a nice set of suppression tuning curves for human ears. And I'd like to know how human ears differ from laboratory animals.

Wei Dong: We're doing two-tone recordings using the OCT and also we start to play suppressors to see how this suppressor, suppress not only the primaries, but also the DPs and DPOAEs simultaneously. So we will hopefully speed up our data analysis process and we'll be back to you soon.

Sonal Prasad: I don't have a question, but I'd like something similar to his comment - regarding OCT experiments. Thanks, Lisa, for bringing that up. Based on Elliott's data, I would also really want to see some images of OCT or measurements on animals which are treated with drugs. Some more stuff like that, too. It's really helpful, and I think that's the direction to go using that. I was very happy with Elliott's presentation, we got to see some.

Elliott Strimbu: A long time ago, we tried some imaging with the furosemide treated gerbils. And any structural changes were too small to be seen. Anders [Fridberger] had some work some years ago with Stephan Jakob, and they showed that if they restored the cochlear potential in their guinea pig preparation, that led to conformational changes within the organ of Corti. But the displacements that they saw were on the order of 10 to 100 nanometers. That's too small to be seen in an OCT in imaging mode. I showed the same imaging that Ellika Fallah did, which didn't have a huge change on the bundles. So I mean any [of] the changes would have to be big enough to be seen. I mean, obviously,

if you gave it a drug that destroyed the organ of Corti, that would that would show up in OCT. But more subtle structural changes are probably just too small to be seen with that technique. But that's where, like the confocal imaging and the traditional histology is very good. Oh yes, but I agree. Many other, you know, perturbation studies would be very interesting and we thought about other things. We've tried a few other things in the lab.

Sonal Prasad: But no, he showed this area vibration that... they were really good and you could see like quite obvious changes. So something similar would be great as well.

Anthony Gummer: So there doesn't seem to be any more comments and questions. I'd just like to, on behalf of everybody, thank Bastian and Wei and [the] local team and his extended team for an absolutely brilliant meeting in a fantastic location and in particular that you have kept this meeting alive for the last five years. Not only kept it alive, but very prosperous, and we thank you very much.