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Discussions of Session 2 — From Molecules to Dynamic Supramolecular Systems

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Ben Feringa:

Welcome back everyone, my name is Ben Feringa as you know now, University of Groningen. So, we learned this afternoon a lot about dynamical systems and complex systems in a more general context. I would like to start with that. We heard that this is a problem, a challenge for us for the coming decades. At least, we think it is a challenge to go to more complex dynamic systems, that we have all these parameters that will influence how such a system will operate and going all the way from structure design to dynamics and to organization, length scales, time scales. Bert Meijer said 'non-covalent synthesis'; we have to discover a whole new field. Do we have the tools available to do this, the methodology, the way we are going to handle that? That is my question to the panel

and maybe they want to react on it. Because we are all trained a bit in traditional chemistry with reactions and the kind of things we do currently. Do we also need to develop new ways on how we think about it, how we measure things, how we do things, what are we missing? And so, to me sometimes (except maybe for the DNA that Andrew mentioned where the designing rules are probably more clear because they are already established for us by mother Nature), we explore them. But how to go from "trial and error" to a bit of design in this field? I would like to ask that and maybe then everybody can comment on it. We start the discussion this way. Maybe I can start on the far left with Bert Meijer?

Bert Meijer:

Thank you very much. For design, I think it's very important what you want to design at the end and not just the molecular structure. And it depends also strongly on the application you have in mind. If you want to use materials that are used in your body or in tissue generation, it's a different thing as if you want to go into energy or another material for mechanical properties. So, it's important to realize what the design should be. The point I wanted to make today in the talk is that, if you go to multicomponent systems and bringing them together, and especially as in some of the aggregation phenomena there's a cooperativity involved, then there are tipping points in which suddenly things change completely. And before we understand this correctly: it is very difficult to design. Now, from the 20–30 years I am active in this field, I have come to the conclusion that: to find out the systems that work always in a good way and to understand how it goes, is difficult. There are many examples, also from our laboratory, that work well but that is a unique part. You can do it one or two times if you do it exactly according to that way. But then, there is another student coming and wants to reproduce it, and it doesn't go. And we have no clue where it comes from. Some of the assembly studies we do, are done perfectly, and then we buy a new bottle of a solvent, and it doesn't go anymore. And it is similar to catalysis, and it is similar to crystallization. But it is not, in the field of supramolecular chemistry, so much acknowledged, that that is a point as well. I think it is very important, before you come to design, to say what are actually the structures that you can use on a regular basis, where it always works. That's also the reason, probably, that DNA origami works nicely, because we know now how that

assembly process goes, at least that's what I think. In the artificial world, it is more difficult to find which ones are working very well. I can tell you that with supramolecular polymers, we have made a very simple one, with a quadruple hydrogen bonding unit, very simple to make, works always and I think, I don't know 20 – 50 laboratories around the world are making and using that molecule as well. So that's a robust system that always forms a bond with a certain strength and a certain dynamics. I think we need more of those and then you have to also have them available by Aldrich or whatever other compagnies, so you can make that progress. I am always a little bit jealous of those who are doing catalysis. Someone finds a new catalyst that works and about, I would say half a year later, you can buy it somewhere. And then people are using it, it is used by everyone in the world. In our field it is too much individual. Molecules are used by certain laboratories, you can't get them easily other than that you have to synthetize it completely. So, your motor should be available by, I don't know, *Aldrich* or by the Ben Feringa company or whatever company so that everyone can use it.

Ben Feringa:

I am happy to hear this because, not about the motors, but the fact that you will have the ligands for instance, so you can buy 150 different ligands from Strem or from Aldrich or whatever. That you would have a collection of building blocks that people in supramolecular chemistry and systems chemistry would use to explore more. So that there are more rules sets, based on these building blocks like I think in catalysis or in synthesis etc.

Omar Yaghi:

I'm sort of put in this group, even though I don't consider myself a supramolecular chemist. I have spent all my life linking molecules by covalent bonds, a strong bond, and there is no major reproducibility problem. Some of these things are made by *BASF* in multi-ton quantities, and also you can buy them from *Aldrich*. But what I really want to talk about is more a productive discussion about what we heard from our colleagues in supramolecular chemistry, where they are designing systems that self-propel or are highly dynamic. What is needed is directionality and purpose. And what I was saying to my colleagues like Bert is that, to do that, you need reticular chemistry. And I don't mean that they should turn and come back

tomorrow and occupy my session. But what I mean is that I think you can get the best of both worlds by coupling the supramolecular onto that reticular grid. Imagine a system that they are working on or a molecule that is dynamic or whatsoever. By attaching that to a grid that, let's say, I make, you're attaching let's call it "heterogeneity onto order". And so now you have a complex order that you can potentially design to have molecules moving in a circuitry or in a direction in a purposeful way. You now can imagine a catalyst or a substrate, moving in a circuitry and visiting different catalysts along the way. Well, you need a grid for that. This thing needs to be moving on an otherwise ordered system, but itself could be highly disordered. I think that's where a lot of the systems that we heard could work a lot better. Otherwise, jokingly I said to Bert, otherwise you're making goo, and in noncovalent synthesis of goo and this stuff, using multi-step non covalency will produce even more goo. So, I think that, by superimposing this on a grid, these two areas are ideally suited to be coupled to produce beautiful systems.

Ben Feringa:
You are making life not easier for us because I heard from Bert, balance robustness versus responsive behavior and from you I hear now, balance order and disorder, but Nathalie probably has the answer.

Nathalie Katsonis:
One thing I can say about purpose and directionality in molecular systems is that if we look at concepts from the biological world, that's typically something that chirality brings, so that's probably something to look into: 'chirality at all scales'. And probably another thing is ratcheting mechanisms, that give directionality and purpose to systems of functioning molecules, in addition, of course, to other options. Now, to come back to Ben's question. So typically, movement is an emerging function that emerges in a very narrow parameter space, a narrow range of parameters. And in that sense, it's very difficult to design it. It's not actually a property that comes by design, but essentially a systemic property. And that's I think how the concept of systems chemistry emerged and probably systems chemistry requires different tools than classical chemistry. One of the tools is automatization, so that we can vary a broad range of

parameters in parallel. And maybe also something that we need to consider is how to connect the molecular world to the macroscopic world. So we have techniques that characterize materials and techniques that characterize molecular structures but to characterize both worlds in a dynamic fashion is, I think, quite challenging. There are, I think, very exciting developments, not from me, but in the microscopy world at the moment, which, I think, will allow us to really move forward. And one last thing, I think also it is not a technique that we need but maybe a different mindset. It is that traditionally we look at the chemical reactivity disjoined from the physical environment and if something we can learn from chemical evolution is that, actually, chemical reactivity cannot be disjoined from the physical environment. It's something that we need to learn, really, to look at the chemical reactions and chemical reactivity in heterogeneous systems. It's a good idea to start doing chemistry, not necessarily in solution, not in homogeneous systems, but we need to start thinking about heterogeneous conditions and mixtures.

Ben Feringa:

Thanks very much. That wakes me up again to a point that was made this morning about the interface of heterogeneous and homogeneous catalysis, where for many years we were facing the same kind of issues and questions, about heterogeneity versus homogeneity. Anyway, I go to my neighbour here, Nicolas. Do you want to make a comment on this design versus trial and errors and the faith of our field?

Nicolas Giuseppone:

Thank you, Ben. So first of all, I think that regarding the synthetic tools that we have at the moment in supramolecular chemistry: they are highly diverse, so we can do many things using non covalent bonds from ion pairing, from hydrogen bonds, from halogen bonds, or from Vanderwaals interactions. In addition to that, we have the toolbox using reversible covalent bonds which gave birth to dynamic covalent chemistry and dynamic combinatorial chemistry. So, we really have the power to create a lot of diversity under thermodynamic equilibrium and we are able to synthesize dynamic systems which are robust enough to be analysed for a given period of time, at least in certain conditions. So, for these we have the

toolbox for making dynamic supramolecular systems. We have also many analytic tools from the molecular scale up to the macroscopic one, as Nathalie said, I think we have a lot to learn from physicists, from soft matter, to analyse these systems. Particularly using scattering techniques or rheology aspects, etc. Then the directionality is important. I think we are only at the beginning of the control of the directionality at nanoscale with all these works on ratcheting mechanisms, which are quite complex and still difficult to harness. You have to create order from Brownian motion. This is not something that easy at that scale. But then we are going to enter in complex systems, so, for having complex systems we need multiplicity of interactions, we need multiplicity of compounds, and we need integration of these interactions. And there we come to very complex systems, mixtures, exchanging components, which become more difficult to analyse. So there are two things, maybe, we should concentrate also on function: which function can emerge from a complex system, so we can directly measure the function? The second point, I think, is that we have to be helped by theoreticians: how to design our complex system? It is not only a question of mixing components to extract an important function. We need to know what theoretically could emerge from feedback loops, from a network of reactions and there's a lot to learn from theoreticians on that aspect. And finally, if we want to push them out of equilibrium, you need to inject energy and we need to find relays to transform this energy and fuel the system in an interesting way that can lead to non-linear behaviours.

Ben Feringa:

Thank you very much. For these functions that have to emerge, focus on there. That's a very important message from your side. And 'cooperation', that's also what I think of.

Andrew Turberfield:

So first a disclaimer: I'm a low temperature solid-state physicist by background, so I'm not hampered by too much traditional chemical knowledge. In my field, designing very big and very complex stable structures is almost trivial. What we don't do very well at all is design the pathways by which they assemble, so designing for fully efficient assembly is

something we're just beginning to explore. That's a big challenge. So when we, the community, show you in a cryo-electron micrograph, gorgeous, huge — I mean hundred nanometer dimension — assembled structures, they have been selected. Those are the successes, the failures are stuck at the top of a gel in the well, and we cut them out and throw them away. So efficient assembly is a big challenge. Static structures are relatively straightforward, notwithstanding, dynamic systems are much harder. Because typically when we design complex interacting systems with many components, if we tweak one component we disrupt everything else. So we are developing a toolkit of methods, introducing base pairing defects, doing not entirely obvious things. But it is very hard to design rationally for dynamics and in fact the best tools we have, which are becoming extremely good, are computer simulations. So coarse-grained simulation is the way to go and really the only limitation on that is computing power. We can practically simulate assembled huge systems, but the dynamic behaviour of only very small ones. And, as you know, inevitably, these programs get more efficient and computing power grows, we will become more and more capable of designing our systems through the medium of simulation. So, just on directionality. You've got directionality in time, directionality in space. For directionality in time, you've got to dissipate energy. In our systems, generally that's done by catalysis and control of hybridization reactions. So, in fact, you're using the creation of base pairs as your energy source. That's very programmable, very controllable, very flexible. It's a wonderful system. It's a bit frustrating that we can't interface our system readily to small molecule reactions. We'd like them to go much, much faster, and to use small molecule fuels that you can have present in millimolar quantities rather than the micromolar that we typically use for oligos, so that's a frustration. Directionality in space, that's something actually self-assembled systems made from DNA and RNA come with for free, so we can make a planar, reticular if you like, surface on which to build our systems. We can address every pixel on that system individually because they're all identified by different DNA sequences. So that's one of the aspects of the structures that we make, that's actually very rewarding. Every point on a 100 nanometer self-assembled DNA structure is individually addressable and we can make something walk around it.

Ben Feringa:
Great, as you focused on the dynamics, I have an additional question for you. From a physics point of view, do we have enough tools to study in detail these dynamics? Nowadays, we have time resolved AFM, for instance, which helps us a lot, but there are other tools. Would you ever dream, that you say that or that would help us tremendously in this field?

Andrew Turberfield:
We have done time-resolved AFM. On the right system, it works wonderfully well. AFM works beautifully on very planar systems, but as soon as you have got anything lumpy or three dimensional, then it works very badly. So really, what we would like is the equivalent of time resolved AFM that would work. There's electron microscopy but, obviously, every time you use that you're looking at a frozen, dead system. So yes, something, some tool for three-dimensional imaging, that will give you dynamics. We look at snapshots and that's all we do. And then, dynamics we get with very high time resolution by strapping fluorophores to our structures and using time-resolved FRET. But that gives you very limited information: it will tell you whether two particular points on your structure are approaching each other or are far apart, and it can give you that with very high time resolution. But really detailed three-dimensional structural information is very hard.

Ben Feringa:
Thank you very much. Okay, I want to go to the general discussion, but first I want to ask one more question. But as Kurt Wüthrich is our president, he is allowed to ask his question.

Kurt Wüthrich:
Are you suggesting that kinetic energy of stochastic Brownian motions is funnelled into directed kinetic energy, which is possibly even periodic? This is a fantastic idea. Are we going to solve the energy problem that way?

Nicolas Giuseppone:
So, what I claimed is that the kinetic asymmetry in these ratcheting systems can create directionality, but you need to furnish energy to the system to make it directional, you cannot have it for free. So because you

go against entropy doing that, you cannot solve the energetic problem. You will always need to furnish more energy to your system than what you will recover as an output of your system. There is dissipation, things like that, that enters into play. So I don't say that we are creating energy, we are creating directionality from energy. And then, this directionality can be transduced to other functions in a cascade of processes where you lose energy all the way.

Kurt Wüthrich:
Yes, but the energy is available. At 300 K we have high thermal energy that leads to the stochastic Brownian motions.

Nicolas Giuseppone:
You cannot extract directionality from one base of energy. You need the thermal energy plus another source of energy to bias the random thermal motion in one particular direction. Maybe Ben will correct me.

Ben Feringa:
Of course, in the systems that we studied, that we showed here and also you showed and Natalie and so, of course you put in either chemical energy or you put in photochemical energy. Energy from the light or from a chemical conversion. To make that possible, you have this extra energy to make it propulsing in a certain direction.

Andrew Turberfield:
Well as a physicist I'm forbidden from violating the second law of thermodynamics. The only comment is that obviously, yes, we have external energy input. By playing with low energy chemical inputs, I think you have an opportunity to be very efficient. Blue photons are squandering energy, but low energy noncovalent reactions allow you to rectify Brownian motion in a very efficient manner. So that's some sort of response to the energy crisis.

Kurt Wüthrich:
So, would you only need to lower the temperature of the solvent in order to feed a lot of energy to your macromolecular system? There, I think, would be no problem with thermodynamics.

Andrew Turberfield:
Only if your molecular system has one leg in your cold bath and one leg in the hot one.

Nicolas Giuseppone:
That's right. So if you can have a gradient of temperature at the scale of a molecular motor, yes, but it's difficult!

Ben Feringa:
I would like, before we go to the general discussion, ask one more question to each panel member here. That is a question I often get when I discuss, either with chemists or also with more general scientists and the public: Why do we need molecular systems?

Bert Meijer:
All around us is molecular systems, everything that we use is a molecular system. Many molecules at the same time, if we go to the shower, if we eat, everything is a combination of molecules. And so far, the understanding of making these molecules together into their function and their property is based on trial and error. And I think that's the reason why we have to do this, especially that's the part of the dynamics I'm interested in: to see how you can tune the dynamics, from robust and stable for as long as you want to have it stable, and having it dynamic in order to remove it when you want to remove it. And I think there's an enormous need but it's a material-oriented need, and therefore, it's everywhere. Everything that you use and buy is a molecular system, a combination of molecules and if you see how the messenger RNA vaccine is made by surfactants and messenger RNA, it's a beautiful way of doing, but it's also a bit of lucky that it works so well and we have to realize that only 8% of the messenger RNA in the cell is active and it can go to 100% if we know not only how to bring it there, but also how to get it released just at the right moment. And that means that molecular system that goes into the cell is responsive to the cell to deliver all the messenger RNA at the right moment. It's a very hot topic at the moment, but it's just an example. It's everywhere to get that control.

Omar Yaghi:
I wasn't sure if you're asking about molecular or extended systems?

Ben Feringa:
No, I'm more asking about the system. And on the one side we have the most complex system, which is probably the cell, with all these functions which are more complex than the whole city of Brussels, I think. On the other side, we have simply hair shampoo that you use for washing your hair in the morning. Still, that's a complex system and you look at all the components that work together there to do something that you get this nice hair, beautiful hair, etc. I mean it is amazing and when you talk with industry, people say to me, oh, yeah, we mix things together and we look at the properties and that's about it. No, that's not entirely true, but it's less complex than the cell, let's admit that. So, this is why I asked when you look at systems, there are different graduations in what we call the system, but it's certainly not one single molecule. They are molecules that do things together.

Omar Yaghi:
I mean, I'm always surprised by the popularity of molecular chemistry. Because for the last 100 years, we've been working on molecules, but yet the world around us, including your own body, requires extended structures like bone structures, right? So, you can't build an airplane from just discrete molecules, from soft matter. I think there's a lot of examples around us that require us to think more about building structures that, well, first protect living systems, but also are used in many applications, not the least of which are transportation, computing, and things like that. I'm not saying that molecules are not important. I'm just saying that the other side of chemistry has been terribly neglected. And we are focusing a lot on molecules and soft systems, when in fact, as I mentioned earlier, if we think about extended systems, be it heterogeneous catalysts or alloys, they are absolutely necessary for the molecular world to operate in a way that would be productive.

Ben Feringa:
I'm happy to hear that. In my opinion it doesn't exclude each other but Bert wants to comment on this.

Bert Meijer:
If you would bring all the molecules out of this room, what do you think will be left?

Omar Yaghi:
Wait, I want to be very clear. Everything is made of molecules, but they're not discrete molecules. Some of them are interacting through weak interactions some of them are interacting through covalent interactions, right? And the latter ones have been used to make extended systems, have been longer neglected, that's what I'm saying.

Ben Feringa:
Wait, guys, you'll get your chance in a moment, you see this is already very interesting and debatable. Nathalie, can you comment on this from your perspective? You work on systems. How would you convince the people that they should work on this?

Nathalie Katsonis:
I don't know how to convince them, but I think we need complex answers to complex questions. So of course, we need to look into complex systems and I think the key here is complexity. Let's say one concept, I think the idea is that instead of taking molecules separately, we want to make them work together in space and time so they can become more than the sum of their parts. And when we find a way to make molecules more than the sum of their parts, I think then we can do a lot of interesting things. But that line of thought didn't bring me that much money so far, so I don't recommend it particularly.

Ben Feringa:
Okay, to getting grants, that's another problem, we can discuss later. But okay, maybe Nicolas, you also want to say something?

Nicolas Giuseppone:
So why I believe it's interesting to go to systems is because we want chemical systems to be responsive, capable of sensing their environment, adapt and regulate. And I think for the regulation, you need to have many

interactions in well-organized networks of reactions or networks of interactions. This is what you see in living system, for allostery, what you see with negative or positive feedback loops, this is what regulates the cells for adapting to their environment and finally to evolve. Obviously in living systems you have also to add self-replication processes, etc. Hence if we are able to do that in artificial systems, it will be important for the stability of the network as a whole to be in a complex system. And I think that if we are able to build that from scratch with simpler molecules, we will understand aspects of the origin of life and also we will use these tools to make smarter and more active materials and in that sense, we will create new technologies.

Ben Feringa:
Thank you very much. Yes, Andrew.

Andrew Turberfield:
I'm a physicist, and my colleagues often want me to study simple, boring, periodic systems. I come from the opposite extreme, I ask myself, what could we do? Given that we can make things that move, can walk and move along the track directionally, can pick things up, can make them go, can you construct something by making a molecular machine tool, an assembler? Can you program it? Can you build something that you couldn't build otherwise? Can you make an autonomous agent that would actually be useful medically? Something that would sense within a particular cell, decide whether to do something or not, and if it found a condition, activate something that was therapeutic in nature. All of these things are challenges that you could only conceivably solve, address, not with one molecule but with a complex interacting system. So, complex dynamic systems are, obviously to me, where the interest lies. What are the limitations? I'm sure there are no limitations. It's just a question of time before we gain the capabilities to do all of these things. What can we do, how do we get there?

Ben Feringa:
Thank you very much. Nobody asked me but I fully agree with what was mentioned here. And I want to add where my excitement came, maybe

from a fundamental point of view and that is: we make all these materials, we know all these beautiful molecules and we enjoy that. And then suddenly I realized: how to make things move? Because that is what life does, as Natalie mentioned already, how to repair itself, how to adapt itself, how to respond to input from outside and sense and adapt, etc? And when we made the first molecule that showed some controlled movement by energy input, and we made the first piece of plastic that we cut and then it repaired within 10 minutes, I got so excited that I thought there must be something in chemistry for the future there, you know. So, with that, I would like to open the general discussion.

Peter Palese:
A question for Doctor Yaghi. Is there any commercial product available already, which uses your molecular weaving technology at this point?

Omar Yaghi:
Not yet, but there is a couple of startups that are commercializing that technology. It's only five years old, since our discovery.

Peter Palese:
Can you give us a feeling? What can you say? What kind of direct applications do you see coming first?

Omar Yaghi:
I think for the molecular weaving: it doesn't interfere with the way you make the material, the original material, let's say the advanced polymer or the structural material. It is just an additive and you're adding it at 1%, 2% or 3% maximum by weight. So, it basically does not interfere in the actual process. But, at the nano level, it is distributed throughout the material, and therefore it could then operate in terms of managing the stress on a material in the way I described. So structural materials, anti bulletproof vests, this kind of thing, anything that you can make: where usually with these materials, when you increase strength, you also increase the fracture ability of the material. But, with the weaving, you're able to combine strength with less fracture. And so, it just has,

I think, tremendous implication on materials. Needless to say: also tissues, bone.

Ben Feringa:
Okay, thank you. I think it's an important point.

Chad Mirkin:
So very interesting discussion. I was kind of surprised. To me, this field needs a couple of things. One is a good set of drivers. So, most of what I've heard, is of course, a part of any field, you know: what is possible? Can I make a motor? Is it possible to make a molecular machine, which is an interesting question? But then what do I do with it that ultimately people care about? How do I do it? And how do I use the tools that we currently have? And one of the things that is of course very limiting in this area is soft matter in interface with the tools that were used to process hard matter. So, the semiconductor industry is probably that greatest example of one of the greatest engineering feats in all of time. And it is remarkable but it is not set up to work with soft matter. Well, in fact, most people will run if you'd move towards their fabs with soft matter. So how do you scale it down even further, right? Because you have to, if you really want to make use of many of these types of things. How do you address all of the individual structures? It's very different from seeing things walk on a sheet of DNA, having that sheet of DNA interfaced in a particular way, that I know right over here, one molecular process is occurring and over here, a different one is occurring, and I want those two at a specific position. We don't have tools that allow us to do that. So, it sure seems to me that if you're going to move this field forward, you're going to need to think about: what can I make that would show people this has a lot of legs? Because there's been a lot of kind of gee whiz type of things that have occurred, which again, that's not criticism, is a part of any field. But to take the next step, you really have to think, to do what I call 'a Bob Letsinger experiment'. I used to work with my 84-year-old collaborator Bob Letsinger. He said: "Chad, let's assume everything works the way we think it's going to work. You know, was it worth doing? Can we actually

get to something that the world is going to care about?" I think it's worth doing that experiment now.

Andrew Turberfield:

I haven't mentioned it, because it's not dynamic as an application, but one of the things that is driving what we are trying to do at the moment is the idea of templating molecular electronics, so it is precisely the semiconductor industry beyond Moore's law. And one of the things that has held back the whole field of molecular electronics is that there's no good way of assembling molecular electronic components. And actually, the DNA self-assembly technology is just begging to be used for this. It's a way of positioning things in three dimensions in a programmed way. It is a breadboard, you lay things out in a three-dimensional fashion, and in fact, having got them in the right place, you then wire them up by forming covalent bonds between them, so templated chemistry. So that is a vision. It falls short of your requirement for a gee whiz driver, in an interesting way: if we could do it, it would replace the entire semiconductor industry. And if you look at the magnitude of that statement, you see the problem which is that the activation barrier to getting there, it's just far too high. And I would love it if someone told me what intermediate product we could aim to make, that would demonstrate that technology, without requiring us to replace, you know, a billion-dollar semiconductor fab.

Chad Mirkin:

It seems like you have to do the analysis he did, which was he made a similar issue with respect to CO_2 reduction or the Haber process, coming up with an electrocatalytic version of this. Pick something like the pharmaceutical industry where, again, you don't have such a big barrier. I agree with you, if you try to go head-to-head with the semiconductor industry, you're going to be knocking on a lot of doors with very few opening, right?

Andrew Turberfield:

Yes, I mean, that's the problem I'm posing. I'm just not sure what that industry is.

Bert Meijer:

Obviously, I'm not in that area of moving small objects. But I asked myself the question: if you compare non-covalent bonds and covalent bonds, when is the covalent bond good and when is the non-covalent bond good? In many applications of materials, we have too many covalent bonds that are so robust that they will stay there forever. And, with the knowledge that we now have about supramolecular chemistry, we can make molecules that are smaller, have more specific interactions that you can tune, in which the balance between covalent bonds and non-covalent is changing to more non-covalent, in which the dynamicity of their temporary use is much higher. So, for instance, our materials are used in tissue engineering, in human beings, because we can tune the mechanical properties and the degradation independently of each other and, therefore, the body can take care of removing that material just at the moment that its role is taken over by the cells. I think that is also the same for what I had mentioned just before this. If you want to have debonding on demand, which is bond continuously, but if you want to get rid of that strong bonding, you have to tune the number of covalent bonds and non-covalent bonds. And with that, obviously, dynamic covalent bonding is also an option. The whole idea is that you build up three-dimensional material with better control over covalent and non-covalent bonds, this gets you that dynamic. And the same is, as was just mentioned, in the assembly process. My group is working for almost 35 years already on organic semiconductors. And one way of doing this, is to have full control over how the π system is organized in space and for that you need dynamics in order to get the structure fully formed, and then it has to be there as a material. That is a self-assembly organizing process that will be used and if you go to smaller, you have to do it with structures that are better defined than the ones that are used today. As an example, if you have a hole of let's say 20 nanometers and you want by directed self-assembly to make that a hole of one nanometer, you need an exactly discrete molecule to fill up that hole, because if that is diverse in length, every hole has a different composition. And assembly in confined space is a very complicated thing, you get all kinds of different structures. So, you need to have

at the right moment, the right chemical structure for a specific application and I fully agree with you, you need a specific application in order to tune the molecule and then you have to take care that the covalent bond/non-covalent bond ratio is just that what you need for that specific application. And that is new, because polymer chemists actually never did it other than nylons, in a way, and organic chemists were not very interested in materials. So that field where organic chemistry and materials chemists are coming together, is a field that has to do this trick. But it has nothing to do with moving objects.

Yamuna Krishnan:

I have a comment and a question to the panel. My comment is: I think it's very easy to say: what have your jivas done good to you? There have been a lot of ways of looking at DNA nanotechnology as like molecular gymnastics, but I just want to say that it has given us strand displacement, which was the basis of hybridization chain reaction, which very recently -we've all just come through a pandemic- was used for making many COVID tests. So, let's not forget that. There's also DNA sequencing, which is also DNA nanotechnology, and that was used to pinpoint variants of concern that were popping up all across the world and saved many of our lives by informing travel policies. So, before we ask DNA nanotechnology, what is your jivas trick? I think there have been a couple already. And so my comment to the panel is, actually, thank you so much for putting up those five questions. Because those five questions have remained for the past 20 years, when I started out in this field and moved on: how do we control, achieve extrinsic control of nucleation, aggregation, growth and movement in 1D, 2D, 3D and time? To some extent, we kind of try to maybe convince ourselves we have some control, but that's intrinsic control by controlling the shape of the molecule or the composition of the molecule. If we look at how Nature is already achieving nuclear controlled nucleation, aggregation, growth, and all these things in an extrinsically imposed way, we don't fully understand this yet, even by looking at biology. It's usually through multicomponent systems, and many of you have alluded to that, but I just wanted to understand how you see that interfacing happening between systems which give you some level of control but there is not much processivity and robustness, combined with

molecules that give you very nice reversibility but we don't have the level of control in 2D and 3D. I just want to see what your vision is.

Bert Meijer:
Thank you. A short answer actually with a back question. That is, there are many people here in catalysis: So why is there only one example of the Soai reaction? That's a complex molecular system, with EEs close to 0.001 for the catalyst and it becomes 100%. Why is it not general? Something apparently we don't understand of a complex molecular system, or maybe someone knows why there are not more?

David MacMillan:
I think, maybe I'm answering the obvious here, but it's because obviously the product molecular structure influences the subsequent catalyst and so the chances of that happening, the probabilities of that happening are remote and that's why it happens at the level that it happens. It has happened more than once, there's more than one example of it.

Ben Feringa:
I am happy that you bring this up, this multicomponent aspect, because in my experience, but the others can comment on it, if you bring several components together and you have to do this kind of hierarchical organization and then you have also to do the dynamics you know, in adaptive etc., it is still extremely difficult to predict. Look at all our examples that were shown today. Still, a lot of it is based on well-defined components and I challenge everybody to tell me the design principles when you have more than three components for instance, or even more than two, you know, it's tough.

Henry Snaith:
It's fascinating, I'm an outsider to this field. It's fascinating seeing the complexity of these systems and what you're trying to control. And my question, related to some of the previous questions asked, but specifically with respect to the molecular motions or these active moving molecular machines: Is there an understanding of what you have to achieve? Sort of like a roadmap, let's say, towards being able to do something useful with

them or having a key application? And are there applications that we think this would be useful for and has anyone got any idea on the timeline to get there? Maybe someone will say "yes, they are already present".

Ben Feringa:

Thank you very much. This is a very important question that was asked to me many times and I'm sure Fraser Stoddart can give a much better answer to it, because he has very clear ideas there. But there is, I think, the roadmap, there are so many aspects to it. You know, it was mentioned already, directionality, translating for instance rotation into a translation. I showed examples of catalytic propulsion, using a chemical conversion but then using it to transport something, for instance, in and out of a cell, like biology does, or from point A to point B or using it for assembly in a direction manner. This is still a tough, tough one. Omar was mentioning the beautiful extended molecules he makes, which are these framework reticular materials. This could be a fantastic template for showing how you could transport things at nano or sub-microscales and I think this offers tremendous opportunity. So I'm really happy that we are here together with people from different angles coming together to see how we could do this. Because I cannot do this on my own. I need this kind of framework materials or surfaces, modified surfaces, etc... to do that. And, just to give you an example, you could build a trajectory, like in your muscle or in your body where the motors walk over the filaments, the actin filaments; build a trajectory where you balance the non-covalent interactions so that your molecules don't fly bananas everywhere but walk from A to B over a trajectory, keeping to the trajectory and then also transporting something and doing something. I mean, in the next 10 years, I would be extremely happy if my students would be able to accomplish that, because this is supramolecular chemistry *par excellence*, combined with either photochemistry or catalysis and balancing the interactions and then doing mechanical function. We have been working on it for a while, so we are still at a very early stage. On the other hand, looking at applications, we have now the first examples where we have self-cleaning glasses and surfaces, because they are responsive, and they clean themselves. And also, as I mentioned, they're moving and you can move material on the surface, and so there will probably be applications in the next decades

where people will use maybe not our motors — they might be too expensive, but when you know the principles and you have seen Joanna Aizenberg (I showed that on purpose), she has fantastic surfaces where you can have this amplification of motion because she can structure surfaces and then get synchronized motion etc. I think these kinds of materials, when I was in industry, I would keep an eye on that, because I think that will be the first application in my opinion. And many people will be happy if you don't have to wash your car anymore or your window.

Joachim Sauer:
I would like to make a general comment. So, if we would have to prove as a chemist that we understand something, a system, we have to be able to synthesize it. Otherwise, we don't understand it. So, I would see the value there.

Ben Feringa:
I'm happy you make this remark. I think it was already Richard Feynman many years ago that made similar remarks. I really appreciate that. Because, indeed, if we can design systems that have this kind of complexity and have functions, I think it will guide us in many aspects in the field of chemistry. That's my firm opinion. I'm not sure about the application, all the applications, etc. And certainly, yes, we have to think about that, but thanks for this remark, I appreciate it.

Nathalie Katsonis:
I just wanted to mention that I'm not convinced that the field needs a set of drivers to move forward. I think maybe a field needs conceptual innovation and strong concepts and sometimes the drivers are these conceptual innovations. At least that is my feeling, so I wanted to mention that. And maybe something that has not been said and is maybe not super concrete, but molecular machines, biomolecular machines are usually used for anything our body does. And although that's not one specific application, I think that sets the stage for the potential of this approach. And on midterm and applicability basis, I would think about really neuromorphic materials, because we need these kinds of materials if we want to move forward with our technologies. And for learning and

neuromorphic materials, we need active repositioning strategies that operate at length scales that are intermediate between the molecule and the material.

Makoto Fujita:
So before going to a complex system I will simply discuss about the terminology. So to describe the dynamic motion or metastable kinetically driven structures, we often use 'non-equilibrium' or 'out of equilibrium'. But I feel that this is not appropriate. Because, even if molecules are pumped up at their high energy states or if we kinetically trap the metastable structures, they always miraculously equilibrate up to the metastable state. So, just regarding the dissipative structures, we can say that this is 'non-equilibrium' or 'far from equilibrium', but in a dynamic system, if molecules are trapped at a local minimum, molecules are equilibrated there. You don't agree? So, in my feeling, it's not appropriate to use 'non-equilibrium' or 'out of equilibrium' to describe this.

Andrew Turberfield:
It's a question of loose use of the word equilibrium. So, in true equilibrium, yes, you would have molecules in your high energy state and they will be arriving at and departing from that state at exactly equal rates and nothing useful can be done with them. So they may be locally equilibrated, if you only look at the system very locally in space or in energy, or in a configuration space. But clearly, globally, if you step back and look at the system, the system is out of equilibrium, which is how it's driven to do something interesting. So I mean, strictly speaking, I think we're using the word 'out of equilibrium' correctly. I think you're using it correctly in a very limited sense, which is that if you restrict your view just in the vicinity of the molecule that you're looking at, maybe locally, yes, it is an equilibrium but globally not.

Makoto Fujita:
Also, are there any differences between 'non-equilibrium', 'out of equilibrium' and 'far from equilibrium'? We need some clear definition for these terms.

Ben Feringa:

Yes, I would agree with that, because there is a lot of discussion and there is a lot of use of these terminologies, maybe not at the correct manner. I agree with Andrew on this point when you look at the thermodynamics and kinetics of the system. But, definitely, we need maybe to clarify this, and to the community, maybe we should write a perspective on that to say: what are the correct uses of this, and where are we heading for? That's maybe an important message, here, for all of us.

Andrew Turberfield:

It's a bit like the word symmetry. I mean, strictly speaking, something is either symmetric or it isn't. There is no close symmetry, I mean symmetry is absolute, is mathematical. And I think the same is true of equilibrium. You can always retreat to absolute rigor. Equilibrium goes with the principle of detailed balance and if you haven't got that then you haven't got equilibrium.

Jack Szostak:

So a question and maybe a challenge, primarily for Andrew, but maybe for other members of the panel. You have shown us very impressive, extended, well defined but static structures, and I would be interested in the question whether you could make something like a cytoskeleton that is extremely dynamic and controlled out of nucleic acids instead of out of proteins. What do you think is needed to get to that goal?

Andrew Turberfield:

We can. When I say 'we', I mean the field. It depends on what length scale you're talking. We're okay on a length scale of 100 nanometers, and maybe up to a micron; bigger than that we don't do very well at all. We can actuate single hinges on that length scale, I mean, if we try. But, slowly, we could sort of diffuse in signal molecules which could make things bend and unbend. So we can do something, but it's crude. We could make the cytoskeleton for something of the size of E. coli and we could actuate it, but not with a very great degree of local control. Certainly not with rapid control. And we could do that now. The question is precisely what challenge you're setting for us.

Jack Szostak:
Well, thinking about early stages in the evolution of life, you would want something that would help to control cell division for example. And I think that probably evolved with RNA machinery, but it would be nice to see a demonstration, something dynamic in the lab.

Andrew Turberfield:
I don't think that's totally impossible. I think knowing what we know now, we could give that a good go. But the signalling, I mean the energy input, would be crude and slow. We couldn't power that with a small molecule reaction. We could power it with strand displacement reactions.

Jack Szostak:
So the challenge is bringing in chemical energy into the system.

Ben Feringa:
Now I have a question to you, and maybe I should ask this question at your session. But why should we be then limited to these few molecules that Mother Nature uses, because we have unlimited possibilities. You have seen already examples in this field of supramolecular. So why should we design it based on an artificial molecule?

Jack Szostak:
I totally agree. There are several people in the field trying to develop genetic polymers out of completely different molecules and if you could build other parts of a synthetic cell that way, that would be great. But at least we know that somehow life got started using things like RNA. Maybe it's an easier challenge.

Ben Feringa:
But there could have been other try-outs, no?

Jack Szostak:
I doubt it.

Ben Feringa:
You doubt it? Okay, we will discuss this later.

Bert Meijer:

It's a very good question, but I like to see it from the extra-cellular matrix. There's a journey ongoing to make a substitute for matrigel in order to go to stem cells out of organoids. That is a journey that started something like 20 years ago and the progress is slow, but they are coming closer and closer to materials that really grow the stem cells into small organoids by totally artificial ways. But I have to be careful because it still has oligopeptides that are synthesized and put into it, but it is coming closer and closer to that and that would be a huge advantage because that matrigel is always inhomogeneous, every time is different and all of the cell biologists would love to have this on a large scale. The progress has been enormous the last couple of years. It is not inside the cell but outside the cell, but it may be equally important.

John Sutherland:

So, a question to the panel is: How would you build in evolvability, in particular evolvability using phenotype/genotype linkage? If you can do that, you can recapitulate biologists' greatest trick, which is systematic variation and finding the best solution.

Ben Feringa:

I am not a cell biologist, but I have colleagues here that are more knowledgeable in that field than I.

Andrew Turberfield:

I am not sure I'm here to give that sort of answer. One application that I really do think is worthwhile pursuing is the synthetic ribosome angle. The idea there is to make some sort of crude molecular machinery out of DNA or whatever comes to hand, I don't care, that is genetically programmed to again pick monomers from a pool labelled with a bit of DNA, which is the analogue of a tRNA. So the vision is that you have a soup of monomers for real organic chemistry. Each one is covalently attached to an oligo, which identifies it. Our crude molecular machinery will be programmed by a synthetic gene, with codons that aren't triplets, they're probably 10-mers or whatever. It has our own structure, our own format, but the instruction tape, the gene, tells the machinery in which sequence

to concatenate these monomers to make an oligomer. And if we can make a 10-mer, that's probably good enough, out of 10 components. So, if you can do that, you can make huge libraries of totally unbiological oligomers with synthetic backbone linkages and totally non-natural side chains. And in that vast chemical space, which has never been looked at, there must be drugs and catalysts and other useful things. If you can do that, you can do evolution, because you can cut, recombine, mutate our synthetic genes. Having discovered something halfway useful, you can recapitulate the synthesis and do it better.

Ben Feringa:
And maybe I add one aspect to this discussion. Now, maybe I'm not in the genotype or phenotype business, but what we did, for instance, is we put our rotary motors as a mono layer on surfaces and then we grow stem cells on it. Stem cells are very sensitive to mechanical force and using these stem cells, we could control, using these rotary motors autonomously, powered by light, we could use the outgrowth of stem cells and the differentiation, to some extent. And at the level of the DNA, at the level of the protein expression and the anchoring to the surface, it affected the stem cells and depending on the rotary motion, you could differentiate stem cells. This is the stage where we are now. So, there are different options, I think, in this in this field.

Kurt Wüthrich:
I'm curious to hear from Andrew, whether he sees relations between his work on nucleic acids and DNA libraries, which have a big impact already in many areas of chemistry.

Andrew Turberfield:
I'm not sure what you mean by "DNA libraries". Are they these combinatorial libraries of small molecules, DNA encoded?

Kurt Wüthrich:
Yes.

Andrew Turberfield:

Right, so the answer I just gave to John Sutherland was related to that. So yes, our projects, our aim to create a system which works as a synthetic ribosome is related to the idea of a DNA encoded library. It's a special case, because it's based on molecular machinery reading a program or reading a gene and synthesizing the corresponding molecule. It has the additional property that you can do exactly what John asked us to do, which is to evolve. So rather than just have a static library of interesting things, which are identifiable through the attached DNA, if you have a genotype-phenotype relationship, if the label actually codes for the synthesis of the product that is labelled, then by mutating or playing around with the gene, with a label, you can change the product. And what that means is that you can do exactly evolution, you can first create a library of 10^{12} products and select two things from that, that might be interesting. Take their genomes, recombine them with themselves and with all sorts of other rubbish you happen to have selected at the same time and you can begin to do exactly what biology does, which is to evolve. So yes, I mean that the synthetic ribosome project that I described is a special case, but a very powerful case of a DNA encoded library. Does that make sense?

Kurt Wüthrich:

Well, I mean, synthetic DNA libraries have already a big impact, and I'm sort of surprised that you're not more directly involved with your work.

Andrew Turberfield:

Well, I came at the subject from a different angle. I'm not a chemist by background. I'm more interested in mechanisms than educated in chemistry, which is why I'm doing what I'm doing.

Daniel Nocera:

I want to return to one of your questions about tools. So when I went to graduate school, I had to read out Hertzberg and I used to do Franck-Condon analysis just to figure out what my excited state looked like with the photon. Now my students just write a proposal to the advanced light

source, they bring the molecule, they use the LASER and they actually just get the structure of the excited state. And right now, science is on a nexus with these light sources. So Argonne National Lab and Simon Billinge at Columbia, with the power of computing, they can accelerate Monte Carlo and then with the light source and time resolution, they're almost on the verge of getting structures of molecules in solution, dynamically. Have any of you tried yet, to PDF with an advanced light source to actually get the structures of the dynamic system?

Ben Feringa:
From my own perspective, from our library of motors, yes, we have done it. So far, we do femtosecond LASER spectroscopy to look at this. But indeed, the combination now of the modern, theoretical methods to work on the excited state energy profiles and the landscape, and at the different pathways, etc. together with these laser techniques, you can do amazing things. So recently we submitted a paper, or it is accepted now, where we have boosted the quantum efficiency to 70% by simply doing exactly what you say, using these theoretical methods to tune our excited state profile and to get away from dissipative pathways, etc. So, I think there is a lot to be gained there if we revisit the energy landscapes, and probably maybe David wants to comment on this, also for catalysis, you know, for the redox catalysis, etc. There must be still tremendous opportunities there.

Daniel Nocera:
I guess the thing I was also referring to was with PDF, pair distributional functional analysis, they are literally able to put molecules in solution, they are basically getting the X-ray structure of the molecule in solution. It seems like this field could really benefit from basically getting structures of molecules in solution, and this is literally due to this computing power and the intensity of the light sources for scattering.

Ben Feringa:
I'm happy that you mentioned it. I think there are tremendous opportunities indeed.

Clare Grey:
Just a comment, talking about the PDF, that gets so complicated so quickly. I mean, I am aware of Simon Billinges work, but I agree with you that if you have a light as a trigger to change a conformation, then if you look back at to say the work of Phil Coppens or others, then you start to be able to look at differences and then it becomes interesting. So I think, it's an area where there's more to do. I'm not sure in its current state, but I agree that in general, yes.

Daniel Nocera:
That's on the verge, clearly. And I think with some of these very well-defined molecular motions and motors.

Clare Grey:
Well, some of Omar's systems where there's more periodicity.

Daniel Nocera:
I don't want too much periodicity. I mean, that's where the power is coming out. It's literally without the need for periodicity. Some of this hasn't been published, some has, the beginnings of it, but they are literally getting structures of molecules in solution.

Ben Feringa:
I would love to see it, yes. This is great.

David McMillan:
I was just interested in a slightly different tangent and maybe this is a boring question, but I was interested from the panel to sort of talk about, aspirationally: What do you imagine or think about? What will be the things that you could achieve, and you think is realistic to achieve within five years? And to pursue this is, number one: I always think it's difficult when I see a supramolecular talk because there's a lot of aspirational components, which I love, I can't tell the timeframe. So I'd love to sort of hear what you think about the next five years. And the second part is a quick Bob Grubbs story. I once saw Bob Grubbs being interviewed and the

interviewer asked him: “What will you be doing five years from now?” and he said: “well, if I knew that, I’d be doing it now”.

Ben Feringa:
This is a great question, Dave, so maybe I ask every panel member what their aspiration is, what their dream is. Let’s start with Bert.

Bert Meijer:
So, our materials are now in the last clinical phase, and I hope they will really be used in human beings in the coming five years, based on supramolecular materials. And the other one that I really hope is if there is a way to use spin-controlled chemistry by using chiral electrodes. Not saying that it will be useful, but I don’t know whether that’s true or not true, or it will not work at all.

Ben Feringa:
Thanks, Bert.

Omar Yaghi:
I would say that, again, I encourage the supramolecular to combine with the periodicity, so if you do that, I would say that the opportunities are endless in terms of systems. First, they can sort molecules very well, because they can design complexity and when that complexity is superimposed on the periodicity, it gives it structure and control in the metrics of that structure. And also control of the ratio of those supramolecular elements and their distribution on the grid. So once that system is able, let’s say, to fold, let’s say turn from a sheet into a pipe or any other shape, I would say that’s possible within five years to have a system that can sort molecules. I don’t want to say a system that has a circuitry as I described before, but I think that’s more complicated. I think directionality and where the substrate is going is quite doable. I mean, ideally, I would love to have a crystal that is made from, let’s say, a MOF or a COF onto which you have in the pores superimposed a supramolecular ensemble that then can separate air into different components and so oxygen goes along that pore, nitrogen goes along this pore and water or CO_2

comes out of the third pore. I think that this is not out of the realm of possibility.

Nathalie Katsonis:
A PhD in the Netherlands is four years. In five years, I hope I have educated good chemistry students. If I do that, I'm already happy. Sciencewise, I hope I understand better the origin of purposeful movement in chemical systems.

Nicolas Giuseppone:
I agree, maybe the field is a bit curiosity-driven at the moment with no clear applications and it is important to make something that we cannot make by other means, to prove it is technologically relevant. So, for applications, I think there is room for making artificial muscles for soft robotics so it is clearly an advantage from the forces that we can generate from these machines and the weight of the muscles we can create, so we can reach probably high force/weight ratio, this is predicted by physicists. I think we are not that far from there. We need also to avoid the production of waste so we need also some sustainability in the production of motion. So maybe this is related to the first session of this morning. The second example I would give is the creation of gradients of ions or molecules between compartments by pumping with a molecular machine. I think we are not that far from doing that and such a pumping/storage of energy is interesting for many potential applications.

Ben Feringa:
Thank you very much.

Andrew Turberfield:
So, a PhD or a DPhil in the UK is three years, and I am, if you ask my students, remarkably poor at predicting what they can achieve in three years. But on five years, I reckon we will have wired up and measured, probably at low temperature, a molecular electronic device, not a very sophisticated one. I think we will have printed a pattern on a surface using directed motion of a write-head and the pattern will have nothing to do

with DNA by the time we have finished. It will be proper chemistry on the surface. And I think we will have made a genetically programmed 10-mer from a soup of possible building blocks.

Ben Feringa:

Thank you very much. And I should challenge the whole committee, I suppose, I can also give my dreams. I gave already one, that is to move autonomously over a trajectory, not covalently but supramolecularly, from A to B, hopefully 20 nanometers or so on a filament, or whatever, maybe the kind of structures that Omar makes. And we made already a motor MOF, by the way, where we have the motors as the pillars in the MOF and so control transport, that is one of the other. We will team up to control transport, that you can select which molecules will pass through such porous materials, as active membranes. The other dream is to see how we can make responsive drugs and I put a lot of effort in that now. We build in these tiny machines into drugs, and we were able, lately, to influence the communication between bacteria. Because bacteria communicate with each other to make biofilms and this is really important for the medical field and for the implants and whatever, etc. And recently, we were also able, together with Japanese colleagues, to change the circadian clock in cells, reversibly by four hours. I don't know about your jetlag, it will not be applied to human beings yet, but I think in about 10–20 years from now. So these are my kind of dreams. And my third dream, that I would like to realize: we made already one type of catalyst, an adaptive catalyst that would change and could do sequentially a number of steps. So my dream is a bit to program such a molecule to do a sequence of steps because the catalyst itself adapts and can do step A, step B, step C. That is a bit of a dream, don't ask me exactly how to do it, but this is what I'm dreaming.

And this is actually the last question I wanted to ask, because I think we have to finish sometime. There are people from the biology field and we heard already some challenges from the biology field, but I challenge you to ask, to give us a message: what should we learn from the most complex system which is a cell, or from biology? What is something that we have not discussed and that you would say, please community, take this in your luggage back home and think about it?

Sabine Flitsch:
I was wondering about compartmentalization. If you look at life, you have cells, you have membranes, you can compartmentalize things, you can use membranes as surfaces and so on and I think you can maybe incorporate that into your systems. I am thinking of Hagen Baileys, cells and so on. If you combine your motors with that sort of system, I wonder whether that would give you some better control as well. It looks more complicated, but it might give you better control.

Ben Feringa:
Fantastic that you bring this up, because I think it was mentioned by a couple of people here before in their talks: compartmentalization, and then also dynamic compartmentalization, adaptive, that's what you see in cells all the time. I don't know maybe there are other suggestions?

Donald Hilvert:
My comment goes in the same line as Sabine. In biology, these partitioning events, controlled partitioning events, are really, really important. And it seems to me it would be directly relevant to understanding how these biological condensates form and what their role might be, and maybe one can even learn how to exploit them in new ways.

Ben Feringa:
Thank you so much.

Andrew Fire:
As a biologist who's lived through the last three years, one thing that would be wonderful would be to have a 'semi-solid' media that would in the presence of a defined and highly organized structure, a.k.a. a Coronavirus, form a macroscopic visible change, a singularity that would be visible. So we would be able to quickly visualize the presence in our environment of microscopic particles, with a high degree of organization, so it should allow all of these structures to form. That would be a huge game changer in both real-time medical diagnostics and in keeping the world going during pandemics. So, I'll thank you in advance for doing that.

Ben Feringa:
We work on it. Maybe it will take a bit of time before we do that.

James Liao:
If you want to take this in the biological area, I think the most important thing is what we just talked about, the relationship between the genotype and phenotype that allows it to become evolvable. And I think there are a few people who talk about it. Particularly Andrew, to address this issue a little bit I was wondering: What is your idea to encode this information into whatever you call the artificial ribosome or whatever genetic code of this synthetic steps? Is there any idea what they're up to now, any imagination?

Andrew Turberfield:
Sure! So, most synthetic machinery made out of DNA, which by biological standards is very crude, is driven by DNA strand displacement reactions. So, what initiates such a reaction is simply an invading strand of DNA, which is slightly different from one that it displaces, and these strands carry information. So, I showed you in my 10 minutes talk an example of a DNA computation, or a system for computation, which is driven by a cascade of such strand displacement reactions. You can use a cascade of strand displacement reactions to read the information carried by a synthetic gene, which is just a concatenation of codons which specifies the sequence in which you wish to do your synthesis, to reveal them in sequence, for example, and allow them to recruit from solution complementary sequences which are attached to the building blocks or the monomers that you wish to or to join to your growing polymer chain. So, you know, it's all based on the idea of DNA templated synthesis, which is the promotion of reaction by forcing proximity between reactants, by bringing them close together using attached DNA handles, which are the analogues of tRNA. So yes, it's a strand displacement cascade, and sequential programmed interaction with the bits of DNA attached and labelling the reactants in solution.

Ben Feringa:
Thank you so much. I look around the table if there are not any urgent questions. Of course, we can continue the discussion, but then I think we

do that in the presence of the fruits of biology. Oh, we leave at 6:10pm, then it's time to stop. I would like to conclude here. We had already presented, all our presenters here, a lot of challenges and questions, but I get the feeling that we have a lot more challenges and questions, and you challenged us a lot. Thank you so much, everybody for the contributions to the discussions, all the speakers here, etc. I hope you enjoyed the afternoon session as much as I did. And we look very much forward to the rest of the week. We will continue on some of these issues, I'm sure, and we look forward to a nice reception tonight. Now I give the floor to our president.

Kurt Wüthrich:
I have nothing more to say. Thank you for doing a great job.