## 2019-06 Matthias Heinemann on Yeast, Ethanol and Entropy
## Transcript of Interview with Shelley Schlender for howonearthradio.org

[00:00:00] Matthias Heinemann What do you do.

[00:00:02] I'm a professor for molecular systems biology. I do biology, and I use thermodynamics Thermodynamics is a fundamental law; biology has to obey the laws of thermodynamics.

[00:00:16] Not everybody believes that. As a cell a living cell evolves. Does it still follow the laws of physics and thermodynamics?

[00:00:26] As a scientist I would definitely say yes. They, also a cell has to obey the laws of physics, has to obey the laws of thermodynamics.

[00:00:35] You recently did a study where you applied the laws of thermodynamics to explain a mystery.

[00:00:42] It was microorganism that we called yeast. That's the organism with which you can also use to bake bread. And it's the organism with which you make beer.

[00:00:52] And it makes this thing called ethanol.

[00:00:56] Yes.

[00:00:56] Which it doesn't use itself. It takes in energy and then it makes it into something new called ethanol.

[00:01:02] Yes.

[00:01:02] So, you were wondering why does yeast go to the trouble of taking in energy, not using it for itself and instead turning it into ethanol.

[00:01:12] Yes.

[00:01:12] So it takes up food in this case glucose and it only uses his glucose molecule partly and it dumps it only used half as ethanol.

[00:01:23] It Takes in a lot of sugar glucose.

[00:01:25] Yes.

[00:01:25] That's what yeast likes to eat and after it does that, it uses some to repair itself and have the energy to make more yeast babies . . . divide.

[00:01:35] Absolutely.

[00:01:36] But it goes through all this work and it also has some of this energy that it transforms into a new product called ethanol.

[00:01:44] Yes.

[00:01:44] And then it basically spits it out.

[00:01:46] It spins it out, used to only partly.  And then you could ask yourself a single celled organism that only survives if it makes more of itself with the amount of food that it has, Why would it be so wasteful in dumping out part of the carbon molecule that it has used in an unused way as ethanol.

[00:02:10] It Does seem very wasteful for this little yeast cell to waste all the work it did of eating and then making something that it's not going to use.

[00:02:19] Yes. And then the more fascinating thing is actually that. It's not only this yeast cell that knows that, but it's some other bacteria, other single celled organisms that do the same. And it's even more striking that cells in our body can do the same. The cells in our body are not producing ethanol but they're producing another, we call it, byproduct. And this happens for instance in cancer cells. So it seems that if you look across organisms, microorganisms, but also cells in our body occasionally cells can do this very wasteful metabolism. This wasteful metabolism that led us to think, is there a very basic explanation? And what could be more basic than going back to the basic laws of thermodynamics.

[00:03:14] You'd better explain the laws of thermodynamics now. What are the basic laws?

[00:03:19] Well energy is conserved, so we convert the same amount of energy from here to there. But the quality of the energy that we get will only get worse.

[00:03:31] So the first law that you're mentioning is that when energy comes in you can't make more energy out of it.

[00:03:38] Yes.

[00:03:38] You have to use what you take in.  The second law is that some of the energy never gets used efficiently it doesn't go into work. Instead it gets wasted in this terrific thing called entropy.

[00:03:51] Yes. So every time you do a conversion, the useful energy that you get from the products would be less and less because every time they are generating entropy. So the quality of the energy will get less and less. You fuel up your your car where the fuel has a certain amount of energy you convert is energy to motion your car gets you from A to B. But at the same time you generate friction on your wheels. This will lead to  heat and that is for instance part of the less useful forms of energy.

[00:04:29] Some of the energy is always unuseful and in a car for instance there's the heat generated by the wheels touching the surface of the road. That's not usable energy. There's the heat and pollution generated by an engine especially if it's not working efficiently. Energy that's useful that's taken in. You can't have it go 100 percent into useful work.

[00:04:50] Yes.

[00:04:50] Some of it has to just turn into something called entropy.

[00:04:55] Exactly.

[00:04:55] Entropy is what always wins.

[00:04:59] Yeah.

[00:04:59] One more part of this law of thermodynamics is that when you have this working stuff you want to have as much of it as you can be working. But some of it's always going to be wasteful stuff that you can't use and you don't want that inside your engine. You want it to go someplace else. There has to be a cool spot or a spacious place that the entropy will naturally flow to so that it doesn't get stuck inside the engine.

[00:05:26] Yes. Yeah. So in the cell there's now energy conversion is happening. We use these glucose molecules make new cells and this is conversion of energy and in this conversion of energy we actually produce entropy. And this needs to go somewhere. And what we have now found in our work is apparently the operation of all these chemical reactions in a cell, The rate at which this can happen is limited by the rate with which the cell can get rid of this unuseful forms of energy.

[00:06:00] So we do this too. When we eat we don't just eat and it all turns into something that's useful inside of us. We have a way that our bodies excrete.

[00:06:08] Yeah if you just look at our, we have a body temperature right. This is also originally came from. From the food that we ate which warms up our body. But this is unuseful energy that we get rid of.

[00:06:22] So heat is one of the entropic energies that our body produces.

[00:06:27] Yes.

[00:06:28] OK. So that's how our bodies work. And you're saying yeast is the same way.

[00:06:33] Yeast obeys the laws of thermodynamics what we discussed before, every time we convert energy we produce entropy.

[00:06:41] When we eat we produce entropy.

[00:06:43] Absolutely.

[00:06:44] OK got it.

[00:06:45] Because according to the laws of thermodynamics every time we convert energy and eating is actually converting energy, we produce entropy.

[00:06:54] And then what you found with your yeast is that there's a way to measure what's going to happen.

[00:06:59] We have quantified this energy conversion in these cells and have quantified of how much they would produce entropy. And the remarkable thing is that we have found that these yeast cells would never exceed a certain rate of submitting entropy to the environment of transferring entropy. So that was a finding that we've made that there's apparently an upper limit. At which these yeast cells can operate their energy conversion just like, think about a machine.  If you would buy a machine in the US which is used to be fed with one hundred ten volts and you come to Europe and plug it in our power plus. This machine will probably run so hard that it would probably overheat and break because we have to 220.

**[00:07:48] Because you have 220 volts**

[00:07:48] Yeah exactly. So like a machine that one once you look at at the small print at your manual at your operational manual you know you must not run it harder than at this rate. And apparently cells, yeast  cells in this case, cannot operate their energy conversion that they need to do in order to stay alive. Cannot run this harder than a certain upper rate. So this is what the body.

**[00:08:17] Would they get too hot?**

[00:08:17] Exactly. So our first thought also was that producing entropy is connected with generating heat. So that's what we first thought. That eventually small microorganisms, they would, inside themselves, they would get too warm. And if they would get to warm the cellular functioning, the enzymes that are there, the proteins might get destroyed. That's what we thought.

[00:08:38] So if yeast worked too hard and got too hot from the food it was eating it would it would die!

[00:08:44] That's what we thought in the first place. But doing some calculations it turns out that a yeast cell is too small; it's present in an unlimited bath of water. So this heat would just be gone away.

[00:08:59] Oh that's right. That third law of thermodynamics that if it was just a problem of heat, there's plenty of places that are cooler for it to send the energy to so.

[00:09:08] Yeah.

[00:09:09] Theoretically it could get rid of all of the excess heat it needed to.

[00:09:14] Yeah. So this is still a bit of a puzzle for us and we have some ideas that we now are currently following up on what this really could mean. I hope that it will lead us to a completely new understanding of how the inner workings of cells actually happens. But this is still a bit of science fiction at the moment.

[00:09:33] Well let's talk about what you have learned. There is a middle step where it's not the yeast sending everything out as heat that it doesn't need.

[00:09:39] Yes

[00:09:39] Instead it makes something else called ethanol.

[00:09:42] Glucose comes in at a certain rate into a cell.  The cell is metabolizing this glucose or is breaking it down so all the little energy conversions, and it now feels oh I'm converting so much energy at the moment I'd rather not fully break down this glucose molecule.  I'd rather just dump it before things get bad. Apparently these yeasts, these organisms have learned OK I should now not further break down this molecule, because otherwise things get too messy.  And then they dump it, dump the glucose molecules, half used, in the form of ethanol.

[00:10:31] Ethanol.  Which Is how we get beer and how we get wine Yes that's how we get beer and wine of course the brewers have additional tricks to further convince these microorganisms to use beer they remove the oxygen and then the yeast has no other way to survive but it's still striking that in the presence of oxygen that yeasts cells still produce ethanol.  That has been puzzling scientists for an extremely long.

[00:10:57] That's right. When you make beer or wine you put a cork on it so that it has to ferment.

[00:11:03] Yes.

[00:11:03] But even in the presence of plenty of oxygen the yeast hits a point where they've been gobbling up the sugar and they go, that's it. I can only take this halfway through.  I can't make more baby yeast.  I can't repair my cells. I'm getting in more trouble trying to process the sugar than I'd be if I just accept the fact that it's time to spit it out.

[00:11:24] Yes yes.

[00:11:25] That's how you get extra ethanol that way.

[00:11:28] And is it just because the yeast has to obey the laws of thermodynamics.

[00:11:33] It's the thermodynamics again!  You're talking about biology in the sense of physics and, it's a different way of looking at the world, and you actually think that there's an equation that can help you predict at what point the yeast when it's gobbling up sugar will say, "That's it!" I have to stop trying to use this to make my body better or make babies, and it's time for me to just spit this stuff out.

[00:11:57] Yes. So that is how on a very global level how we observe this how we can apply the laws of thermodynamics to make computational predictions, but of course, cells are so complex, they need to have mechanisms to sense when the rates of entropy production are now very high. So they need to have ways so that they know, OK. Now it's time to open up my safety valve, for spitting out. It's a safety valve.

[00:12:25] And so they don't have a red light and an alarm system that goes off, but they've got some kind of a measure that lets them know. Now's the time that I will survive better as a cell, If I don't try to hoard this stuff in its sugar form but instead I spit it out.

[00:12:40] Yeah like the old steam engines where water, to boil, and there were also safety valves that sort of opened once the pressure was too high.  I think something like this when in the rates of energy conversions are to high then sell safety valve opens, meaning that they spit out food molecules that is half used, because if they would further process this, things would get bad.

[00:13:07] They would get worse for the cell.  Well these silly yeast cells, why did they eat too much in the first place.

[00:13:13] Well apparently if sugar comes into the cell and they first process this sugar in the most efficient way to get most, uh, yeast babies out of it . . . If I stick with your language . . . but then now as we're increasing the rate of food uptake then they rewire, they're working and they start to spit out the ethanol. But this gives them still a bit of an advantage of still being able to make new baby yeast cells. Less efficient. But still gives them an advantage.

[00:13:41] Okay so there's a reason that they don't just say, "I'm full," because it's actually more efficient for them to keep taking in energy.

[00:13:49] Yes.

[00:13:49] And using the part that's most quickly usable.

[00:13:53] Absolutely.

[00:13:53] It's more efficient for them to use the most available part of the sugar energy for repairing their cells and making babies and stuff and then spit out the part that's excessive.

[00:14:04] I could not have summarized it in any better way.

[00:14:06] Oh, you could have, but you let me just now. So in any events, you said that there's this equation that's well known in thermodynamics called the Gibbs equation?

[00:14:17] That's something that Mr. Gibbs, a long time ago, invented, and he came up with the terms of the Gibbs energy, and Gibbs energy describes the useful forms of energy.

[00:14:29] OK. So it's a way to do a calculation that predicts when the useful form of energy will reach its threshold, and a cell will say, "That's it. I'm going to spit out the rest of what I've been doing.

[00:14:41] Yeah.

[00:14:42] OK. Good for Mr. Gibbs.

[00:14:44] If you have a tank filled with gas, and we convert this into kinetic energy, in this conversion, the Gibbs energy would always go down, meaning that with every conversion, we get less and less useful energy, and that is a concept of Mr. Gibbs.

[00:16:22] So you did that huh. But you say ... that's pretty cool that you've proved that this is an equation that applies to this situation of yeast deciding when to spit out ethanol instead of using it. But you said that it applies to other things. Before you start talking about what you think it applies to, may I share with you what I wondered about?

[00:16:42] Sure.

[00:16:42] OK.

[00:16:43] Well I wondered about the idea that we, as humans, are in this time in the world where a lot of people are obese and they're gaining weight in a way that nobody really expected. And there's one theory that says that people gain weight because we're all designed to store weight in case we ever encounter a famine.

[00:17:04] Mhhmh.

[00:17:04] Well that's never really made sense to me because, if that was the case then you would expect people when they're very young to be as fat as possible to survive, because you need people to survive to reproduce. And you really wouldn't expect people as they get older to keep getting fatter because they're not going to be making babies, so they don't need as much fat. What if instead, these poor cells, inside of our bodies, if they get too much energy, they go oh my gosh, we can't send it out just as heat, let's store it in an intermediate place called fat.

[00:17:36] This is really not my field of expertise But in a way the nutrients that are being taken up are then not excreted, but they're also not metabolized, but taken away as fat. So in a way, without having thought about this too much, I at least can follow your argument.

[00:17:53] Because sugar If you just poured a lot of sugar into a cell you would kill the cell, because it's such a volatile thing it'd be like striking matches all over with gasoline around.  A cell has a more stability if it gets converted into something else, and a lot of that gets used for energy. But even if it doesn't get used for energy, it's more stable if you package it in some other things.

[00:18:23] Yes.

[00:18:24] Which is true probably for yeast when it turns it into ethanol.

[00:18:26] Yep.

[00:18:27] Who knows.  We're playing with thoughts here. But you've been playing with thoughts in this in terms of cancer. Tell me about that.

[00:18:32] It's striking to see that if cells in our body, and this is what cancer cells, do they take a glucose at an extremely high rate.  Cancer cells, and this is long known almost hundred years, cancer cells do a very peculiar metabolism where they spit out another chemical.  It's  called lactate.  It's very similar to ethanol.  All cancer cells do that also when they consume lots of glucose at the same time. So this is highly similar to what we saw in this baker's yeast--the laws of thermodynamics as we stated at the beginning, need to hold for everything.  The laws of thermodynamics also hold to cells in our body, hold for cancer cells, and it could be that this peculiar metabolic phenotype, we call it, is also just because of the cancer that is now taking up glucose at a high rate, spits out this lactate, because it would otherwise harm themselves too much if they would further process this unused molecule.

[00:19:32] When we're exercising, and our muscles produce lactate, could that be because it hits that Gibbs point.

[00:19:38] That could also have been because there's been a lack of oxygen that then also forces cells to produce lactate. Just like the beer brewer also brews beer in the absence of oxygen.

[00:19:49] That's right. If my muscles get sore after I exercise it's because I ran out of breath.

[00:19:56] Yes.

[00:19:56] And I wasn't able to breathe in enough oxygen.  That has a lot to do with my muscles getting sore.

[00:20:00] And that was actually for in the cancer field, was for a long time, people thought that cells would make lactate because there would be a lack of oxygen and that's why these cancer cells would produce lactate. But it has been shown that is not the case. And what we offer, and it could be due to the laws of thermodynamics, due to the fact that also these cancer cells operate their metabolism--there's a safety valve.

[00:20:24] With a safety valve, and any other process in the body that is a high energy use process that makes lactate, It may be partly a safety valve especially if it's in the presence of oxygen.

[00:20:38] YEs.

[00:20:39] Well, cancer is intriguing to you. How come? Why is cancer intriguing to you?

[00:20:43] Of course we all know someone in the family who had suffered from this horrible disease. But furthermore as being a very fundamental scientist, interested in the very fundaments, and you started this interview with stating that thermodynamics could be fundamentals of what biology has built on, being a very fundamental scientist, we're sometimes, particularly nowadays, very forced, very often forced to show to society what the relevance of our work is. And of course if you link it to something like cancer, a broader public audience would always think, oh yes this must be relevant.

[00:21:23] How could it help us to have this relevant thing called looking at how our cells metabolize and spit things out in a new way.

[00:21:31] I hope that my fellow scientists would see, Yeah . . .Even though that I'm not working with yeast. But yes the laws of thermodynamics also apply to any organism. If I'm a plant biologist and also plants need to obey the laws of thermodynamics.  That that I hope that I can convince my fellow scientists to say yes what they have found in yeast or microbes would actually also apply to other organisms. But I hope that this will be picked up and will be insightful for my colleagues as well.

[00:22:03] Matthias Heinemann, it sounds like you want to turn on a light bulb that sheds light in a new way of thinking about this, and see what other scientists find out.

[00:22:14] Yes no. I think that this sort of a desire that exists in in every science is that you will aim to uncover something that is useful for mankind that is useful for your colleagues and your colleagues build upon.  I think that is what keeps us awake and keeps us going.

[00:22:33] All right. So we've just had an interview where we have not talked about a miraculous new drug that's being made to cure cancer or cure any other disease that you can think of. We have not talked about creating a brand new engine that does something different. We have not talked about a better way to make wine or beer. But we've talked about something more fundamental, about how these processes might work at their very most basic level. And that might guide people in a new direction.

[00:23:01] That's what I hope very much yes.

[00:23:07] What are your fellow scientists saying about what you're doing.

[00:23:10] I think I had a bit of an unconventional career. I got my Phd in engineering, and my undergrad in engineering and sort of moved gradually into biology because I was really fascinated about life. I approach biological problems, still, with the thoughts of an engineer. I'm always looking for the simple answer because I think I'm not very good in memorizing detail and biolody is full of detail. So I'm always looking for the simple thing. Sometimes I feel in biology, we don't see the forest anymore because of all the trees. What I experience is that colleagues who are open minded who were open or not very not not too dogmatic, they start to, they appreciate this. But of course there are also colleagues who are interested in a single protein with this particular mechanism. And they have a bit of difficulty, that, "Thermodynamics is something that I had in high school and never understood." Yeah? Like like this type of attitude. I see everything. I'm a great believer in simplicity. While evolution is great. What evolution has brought about. But I sometimes feel that iit would help us if we look a bit more fundamental. Biology has to obey the laws of thermodynamics If they're right then biology has to obey them.

**[00:24:34] Do you think evolution obeys the laws of thermodynamics?**

[00:24:35] I think so yeah. But evolution can explore in terms of, possibilities then that are then being tried out and subjected to selection. These possibilities that are offered that are being generated, they also need to obey the laws of thermodynamics. Or have you ever seen. An egg sunny side up to go back.

**[00:25:03] I have not seen an egg that's sunny side up go back to being an egg.**

[00:25:03] It's not possible. That's because the laws of thermodynamics.

[00:25:10] Yeah well thank you for helping us start to crack this puzzle about how to predict when yeast will decide to turn the energy it's taking in into ethanol and then spit it out. And to imagine some of the possibilities for what that line of thinking might lead to.

[00:25:29] Yes.

[00:25:30] OK. All right. Thank you very much.

[00:25:32] Thank you very much.