Forum

Douglas A. Lauffenburger and Heinz Koeppl*

New biological solutions to the many problems of our time

Neue biologiebasierte Lösungen für die vielen Probleme unserer Zeit

https://doi.org/10.1515/auto-2024-0069

Douglas A. Lauffenburger is Ford Professor of Engineering at the Massachusetts Institute of Technology (MIT). He is faculty member in the Department of Biological Engineering, which he co-founded in 1998. In an interview with Heinz Koeppl, Director of the Centre for Synthetic Biology at Technical University Darmstadt, he explains how Biological Engineering differs from traditional bioengineering, what the education program in this discipline at MIT is based on and why we need biological engineering to solve many of our current challenges from climate change to world food supplies.

Heinz Koeppl: *The MIT Department of Biological Engineering was founded in 1998. However, bioengineering has been around for longer. What's the difference?*

Douglas A. Lauffenburger: Bioengineering or biomedical engineering has existed for about 70 years. Yet it was more about medical applications. From the 1950s into the 1980s most of biological science had to do with medical applications and physiology. The only tools available to engineers came from physics and chemistry because biology wasn't ready to be used. But then there were two revolutions in biology. First, the molecular biology revolution in the 1970s. By genetic engineering the insulin gene was put into bacteria, for example, and monoclonal antibodies could now be used to produce biomolecules with specific effects. The molecular biology revolution allowed biology to be a science that engineers could make things out of.

Heinz Koeppl: *That marked the start of the biotech industry?*

Douglas A. Lauffenburger: The biotech industry really started up in the 1980s and the 1990s. The problem was that although we were trying to do something with genetics and biochemistry, it often didn't work. If you put an insulin gene in a bacterium to produce insulin, that's straightforward. But genetically engineering bacteria to clean up the environment, for example, was too complex. We were not yet able to really manipulate these cells in a really predictive way. We didn't understand them well enough yet. Two things are crucial in engineering disciplines: You've got to have a science that you can manipulate to make things out of and you need to be able to do it in a predictive way.

Heinz Koeppl: *And this is where the second biological revolution comes into play?*

Douglas A. Lauffenburger: Exactly, the genomic revolution in the 1990s enabled us to sequence DNA and identify genes. Now we were able to do transcriptomics and proteomics and it was possible to identify hundreds and thousands of components that interact with each other. What's more, this was achieved at such a high throughput that it was possible to use calculations and develop models that contributed to predictability. True biological engineering, an engineering discipline based on the science of biology, could only emerge after the molecular biology revolution and the genomic biology revolution.

Heinz Koeppl: *Were these revolutions also the basis for the foundation of the Department of Biological Engineering at MIT?*

Douglas A. Lauffenburger: In 1998, it just became the perfect time to create our department. Genetic engineering, leading to synthetic biology, and genomics, leading to systems biology, are the two foundations of biological engineering. You put those two things together, and that's what modern biological engineering is. It's focused on a basic science level and has a very broad range of applications, just like chemical engineering and other engineering disciplines. Biological engineers can develop medical applications with stem cells, therapeutic antibodies, things like that. But they can also work in the environmental sector, in agriculture or energy production. Traditional bioengineering was the opposite because there were only medical applications and no identifiably particular scientific basis. And since many bioengineers knew nothing about biology,

***Corresponding author: Heinz Koeppl**, Technische Universität Darmstadt, Self-Organizing Systems Lab, Merckstraße 25, D-64283 Darmstadt, Germany, E-mail: heinz.koeppl@tu-darmstadt.de
Douglas A. Lauffenburger, Massachusetts Institute of Technology, Cambridge, MA 02139, USA, E-mail: lauffen@mit.edu

they just focused on things they could do with physics or with chemistry like a prosthetic knee, an insulin control system or diagnostic imaging. This all has fabulous value for medical applications, but biology offers so many more possibilities.

Heinz Koeppl: *What does this mean for education?*

Douglas A. Lauffenburger: We have to teach our students genetics, biochemistry, cell biology and microbiology. That's what biological engineers manipulate, model and predictively design. At MIT, we want to train students in a particular discipline that will be very robust. We want them to say: "Hey, I can handle any problem because I know my science and I know how to engineer it." Many of the major biomedical engineering departments in the US have a biomechanical track, a bioelectrical track, a biochemical track, and so on. Students make their choices but there's no real focused discipline there. That's concerning.

Heinz Koeppl: *On which basic subjects is the degree program Biologically Engineering at MIT essentially based on?*

Douglas A. Lauffenburger: What our students get is genetics, biochemistry and cell biology. Everyone has to take these subjects. And then we have classes on how to do engineering. We teach them how to analyse and synthesize, but also the thermodynamics and the kinetics, the dynamic and transport characteristics of biological systems. Then, of course, the students have to gain practical hands-on skills. One aspect is working in the wet lab. A student must be able to do genetic engineering, to work with recombinant DNA. A second aspect is they also need to know how to measure what's going on at a molecular and cellular level, for example with microscopy and techniques like that. The third aspect is computational modeling. For this, we offer a hands-on class in programming and constructing models for biological systems. These three practical courses – biological laboratory, quantitative measurement and computational modeling – are really important to the curriculum.

Heinz Koeppl: *Do you have some numbers for us: How large is the Department of Biological Engineering at MIT and how did it develop over time?*

Douglas A. Lauffenburger: At MIT, we're a medium-sized department in the school of engineering, but very healthy and stable. MIT takes in about a thousand undergraduate students a year, graduates about a thousand, and roughly half of them these days are studying electrical engineering or computer science. Mechanical engineering is also very large, with about 200 students a year. At the other end of the scale, we have small disciplines such as nuclear engineering with maybe 20 students a year. In the middle are chemical engineering and biological engineering with around 35 faculty members and 50 to 70 undergraduate students a year. With the current numbers, we're one of the top five on the MIT campus. The enrollment has remained fairly constant over the last ten years, but I expect a hundred students per year over the next few decades. That would be ten percent of MIT students. Right now it's about five percent and that's certainly healthy.

Heinz Koeppl: *Can every department at MIT decide independently of how much students they take in?*

Douglas A. Lauffenburger: The total number of 1,000 undergraduate students is set by the MIT overall, regardless of what they might major in. We have no control over that. We can't go out and try to get more students into our department. We have to wait and see who shows up. In their first year, students don't even have to choose a major. For the next year, nobody of us has any idea if there will be 20 or 200 students. In our department it's kind of stable between 50 and 70. That's simply an empirical fact.

Heinz Koeppl: *How much is research and education at MIT currently dominated by computer science and artificial intelligence (AI)?*

Douglas A. Lauffenburger: I don't know what it's like at your institution, but here AI is in almost every sentence. MIT is currently so dominated by these things that all students think they have to major in computer science, as if the world only consists of Google, Microsoft and Amazon, who only hire people who can do programming. I think that is temporary, it's really not the only career path nor the best for many students.

Heinz Koeppl: *What professions do graduates of biological engineering work in?*

Douglas A. Lauffenburger: Our students can go into therapeutic biotech/pharmaceutical industry, the medical devices and diagnostics industry, and also in the fields of agriculture or nutrition, energy or materials, or national defense. This is a much broader spectrum of opportunities than that of traditional bioengineers who are by and large limited to a medically related industry.

Heinz Koeppl: *To what extent can biological engineers solve man-made environmental and sustainability problems?*

Douglas A. Lauffenburger: The many problems and challenges the world faces were a further motivation for founding the department. Technologies based on physics and chemistry have done a lot of good, but clearly weren't able to solve all the challenges satisfactorily. Otherwise, we would not be in some of the situations we are now in terms of sustainability, environment, and so on. Bio-based technologies might be able to do some of these things better. We will see in the next few decades whether biological engineers will be able to solve these problems. There are already some examples. Christopher Voigt, for example, who is now head of our department, has founded a company (Pivot Bio) that is trying to replace chemical fertilisers by genetically programming soil microorganisms to fix nitrogen from the air. It looks like it's working, that's a great example! Another question is: Can we grow synthetic meat instead of cows? Can we take a cell culture in the lab and produce meat from it? There are interesting approaches to this, and some companies are already working on it. There are now new biological solutions to many of the problems of our time. Some will become prominent, some may not work out economically, but that's no different from other disciplines.

Heinz Koeppl: *I guess your department also has some industrial collaborations.*

Douglas A. Lauffenburger: Countless! If you walk around the Cambridge area and even now most of Boston, it is densely populated with big, medium-sized and small companies. It's a very, very rich and stimulating environment for industrial research and collaborations, for student networking, for finding jobs and starting up companies. That's all part of the ethos of MIT which wants to have an impact in the real world. So, the collaboration between our faculty and industry is strong. A lot of them are student driven. We have, for example, the MIT biotechnology group, put together by students but with some faculty advisors. I was the faculty advisor when they started it. They have around thousand members now, undergraduates, graduate students and postdocs. They organise all kinds of events and outreach with industry speakers, both on and off campus, for example as dinners. Our students are really interested in what their careers and their jobs might be.

Heinz Koeppl: *What do you think are the most promising research topics in the field of biological engineering?*

Douglas A. Lauffenburger: To me a big one is agriculture. The biggest challenge of our planet is feeding itself. Of course, in Western European and North American countries, that doesn't seem to be so important but it's a worldwide problem. How can we grow plants better, especially with changing temperatures, changing water, salinity and all of that? How can we use biological technologies to improve agriculture? Another huge problem is infectious diseases. Again, we don't think of that so much in North America and Western Europe, although we all saw Covid and we still have HIV, but in other parts of the world there's also malaria, tuberculosis and Ebola, Lassa and Dengue fever and other infectious diseases. Most of the deaths worldwide actually come from pathogens. We've got to find better vaccines and treatments. I put that right up there with agriculture and nutrition. And from a more methodological sense the biggest need goes back to what I said earlier: How can we be more predictive? Can we design an energy system with biological technologies that will be efficient and won't cause any environmental damage? The biggest problem in biological engineering still is that we are not good enough yet in prediction. That's a high priority for biological engineering research and education. Yes, think of cool technologies, but you must make them predictive. Otherwise, people are not going to trust them.

Heinz Koeppl: *But we must acknowledge that we will not understand the full complexity of biology for a long time yet. So, we have to build something that is so robust with respect to any kind of perturbation that I don't even know yet.*

Douglas A. Lauffenburger: That's very well said. What's hard about biology and biological engineering is not necessarily that it's complex. Many physical and chemical processes are also complex. But the dimension of complexity in biology, and you said this very well, is what we don't know. Whether it's the components or the interactions, the ratio between what we don't know and what we do know is so much greater in biology than in chemistry and physics. I'm not saying it's zero in chemistry or physics. But in biologically based technologies so many things can happen that we are just not even aware that they're part of the influence. That's the biggest difference to other engineering disciplines. We do systems modeling to support the development of vaccines or things like that. But you're right, if we're still heavily influenced by unknowns, we can't settle on a single optimal solution.

Heinz Koeppl: *Manmade engineering is based on assembling things from different, well-characterized parts. This is somehow relying on modularity in the sense that the functionality of a part isn't changed. Otherwise, the function of the entire assembly cannot be predicted. The function of the screw is not changed by screwing it into some larger object. It always remains the screw. But is that the only way to do engineering? In biology there are crosstalks everywhere due to, for instance, nonspecific binding of regulators and whatever. Is modularity the right design principle?*

Douglas A. Lauffenburger: The essence of life is adaptability. In living systems things have to run under different conditions. In biology, a screw is not just a screw, it has so many other functions. What's on the head? What's on the sides? That really matters because it's going to interact with other things. Modularity means being modular across many dimensions. Biological systems are often influenced by the context. What will happen if you put the cells in a different media or on a different surface? In biological engineering, it might be counterproductive to completely separate things from context. The whole point of a biological system is to respond effectively to a different context. If I separate everything from context, then I'm not allowing that to happen. We need to model the systems that we are building. And from successful models we can extract some theoretical ways of looking at these things. Think back to electricity. Now we know how to design a resistor and a capacitor but until we actually had models for the physics of current flow, it was not evident how you could put things together. Maybe modularity is the paradigm we follow until we had come up with something better.

Heinz Koeppl: *Today, you and I can develop things on a molecular level, on the nanometer and micrometer scale, but that's not enough. People in architecture or construction are interested in macroscopic objects, for instance biomaterials, so the innovations they need are on the length scale of meters. How can we build a consistent education program for biological engineering across all those scales?*

Douglas A. Lauffenburger: It's true, in our degree program you mainly learn how to design at a molecular and cellular level. Because that's where the mechanisms are located. If you then go to a multicellular level or beyond, you have to specialize. A tree is different from a liver, is different from a rice paddy, is different from a tank of algae or from energy production. We all need to know how to predictably model things at the molecular, cellular, multicellular level and above to study ecology or liver physiology or algae, botany or other things. The higher levels require more specialization.

Heinz Koeppl: *But the bachelor in Biological Engineering is still based on molecular biology?*

Douglas A. Lauffenburger: If you start at the top, you don't really get the tools for biological engineering. If that liver doesn't work well enough or that corn doesn't grow in hot temperatures, you can't do anything about it until you get down to the cellular and molecular level. So, all bioengineers need to be very familiar with the molecular and cellular level. Then it's up to their application interests, and that can be something for a Master's degree or a PhD, to take it higher to whatever domain they want to apply it to.

Heinz Koeppl: *… and to whatever problems they want to solve. Let's hope that biological engineering paves the way to a sustainable future. Thank you very much for this interesting and inspiring conversation.*

Research ethics: Not applicable.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no competing interests.
Research funding: None declared.
Data availability: Not applicable.

Bionotes

Douglas A. Lauffenburger
Massachusetts Institute of Technology,
Cambridge, MA 02139, USA
lauffen@mit.edu

Douglas A. Lauffenburger, PhD is Ford Professor of Biological Engineering, Chemical Engineering, and Biology at the Massachusetts Institute of Technology. He is a member of The David H. Koch Institute for Integrative Cancer Research and an Affiliate of The Ragon Institute of MIT, MGH and Harvard as well as a member of MIT Center for Gynepathology. He received his B.S. in Chemical Engineering from the University of Illinois and his Ph.D. in Chemical Engineering from the University of Minnesota. Prior to coming to MIT, Prof. Lauffenburger was a professor at the University of Illinois and the University of Pennsylvania and a visiting professor at the University of Wisconsin. Prof. Lauffenburger has also served as a visiting scientist at the University of Heidelberg, Germany.

Heinz Koeppl
Technische Universität Darmstadt,
Self-Organizing Systems Lab, Merckstraße 25,
D-64283 Darmstadt, Germany
heinz.koeppl@tu-darmstadt.de

Prof. Dr. Heinz Koeppl received the M.Sc. degree in physics from Karl-Franzens University Graz, Austria, in 2001, and the Ph.D. degree in electrical engineering from the Graz University of Technology, Austria, in 2004. After that, he held postdoctoral positions at UC Berkeley and École Polytechnique Fédéralede Lausanne (EPFL). From 2010 to 2014, he was an Assistant Professor with ETH Zürich and the Group Leader at IBM Research Zurich, Switzerland. Since 2014, he has been a full professor in the Department of Electrical Engineering and Information Technology, Technische Universität Darmstadt, Germany, where he is also directing the Centre for Synthetic Biology. His research interests include stochastic models and their inference in applications ranging from communication networks to cell biology.