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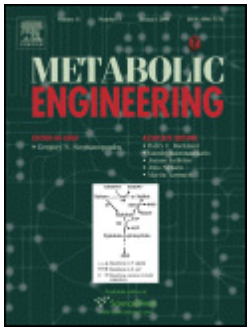

Metabolic Engineering

A Featured Journal from *Essential Science Indicators*SM

In a recent analysis of Essential Science Indicators *data from Thomson Reuters, the journal* Metabolic Engineering *was singled out as having the highest number of citations among journals in the field of Biology & Biochemistry upon entering the database. The journal's current record includes 255 papers cited a total of 3,173 times between January 1, 1998 and October 31, 2008.* Metabolic Engineering *was founded in 1999 and is published by Academic Press, an imprint of Elsevier.*

In the interview below,* ScienceWatch.com *correspondent Gary Taubes talks with editor Dr. Greg Stephanopoulos, about the journal's history and growing influence in its field.

SW: What is metabolic engineering, precisely, and can you tell us a little about the history of the field?

The field of metabolic engineering began to emerge in the early 1990s with the advent of recombinant DNA technology and the realization that microbes could be genetically engineered to become, in essence, little chemical factories for the production of fuels and chemicals. However, the idea of engineering microbes for fuels and chemicals production did not get a lot of attention for about a decade after that because most of the focus was on medical applications. With the change in the landscape of energy supply and production three or four years ago, now there's a lot of interest in using microbes for utilization of renewable resources and making fuels and chemicals from them.

SW: When was the journal *Metabolic Engineering* founded, and were you the founding editor?

It was started in 1999 and I was one of the three founding editors (Professor A. Sinskey and M. Yarmush were the other two). There had been a series of events leading up to this: one was a conference that used to be called something like "Applications of Recombinant DNA Technology." I was asked to chair that conference back in the mid-1990s and I thought about it and decided that this title didn't make a lot of sense. The natural title for the conference was "Metabolic Engineering." So I contacted the stakeholders of the conference and they agreed to change the conference title, and this is how the Metabolic Engineering conference series got started. It's now a biannual event and we're currently in the eighth edition.

Once the field started getting a lot of attention, we thought about starting a journal. We talked to the people at Academic Press and they were very enthusiastic about it. Then in 1998 I published a book on metabolic engineering and all the pieces were in place.

SW: How would you account for the excellent impact factor of your journal?

I have an interesting story to tell you here. Like all journals, this one was not listed in the main indices for the first two, three years. And despite my insistence, there had been a lapse on the part of the publisher to apply for listing the journal with *Journal Citation Reports*® and the main indexing services. This is a lengthy process and takes close to a year. Then after the journal is listed, the formal process for accounting for citations gets into place and the journal eventually gets an impact factor.

"…metabolic engineering does not go unnoticed any longer."

In our case, at the end of the year prior to the year that *Metabolic Engineering* got its first impact factor, I had a discussion with the publisher, pushing them to apply for these indices, but there were some glitches in the system. We finally got them resolved, and we were going to apply, when I was contacted by people from Thomson Reuters, telling me they had observed unusual traffic of citations for the journal, therefore they decided to include it in their databases, and in just six months we would have an impact factor. So all it happened automatically and we never actually had to apply and provide all the supporting materials, etc. And, nowadays, of course, if you're not listed in these services, you don't have an impact factor and it's very difficult to attract good-quality papers.

SW: What do you think caused that unusual traffic?

A few reasons. The first, I think, is that there was a lot of metabolic engineering-kind of work going on. Namely, following some key developments in applied molecular biology, people began to apply genetic modulations very broadly, knocking out genes, deregulating genes, doing lots of molecular, genetic level manipulation, with the goal, always, of improving cellular properties for a particular purpose, such as overproducing a useful product. The possibilities were suddenly infinite, and as a result, there was a lot of metabolic engineering research going on. In that environment, it is only natural that people wanted to know what happens when you do these kinds of changes in cells, particularly people in industry.

A second observation is that before we had even obtained our impact factor, we noticed an unusually high rate of downloads per paper, compared with the other journals in the Academic Press database. That download rate actually continues to be very high and, unfortunately, it's not quite captured by impact factors, because we suspect many of the people downloading papers are in industry and those people don't write subsequent papers; they write patents.

SW: The most-cited papers from *Metabolic Engineering* date to 2001 and are on the subject of C-13 metabolic flux analysis. Do you think these could have been a driving factor?

That's a very likely possibility. Indeed, the use of isotopic tracers like glucose labeled with carbon isotopes—C-13, for example—is a very important method that people use to probe metabolic pathways. If you are looking at a metabolic pathway, from a biochemistry book, it gives you the impression of a street map. As such, it indicates what route you can follow to go from point A to point B but you have no idea how long it's going to take to do so. Such maps are very static. Your travel time depends very much on traffic, and the map doesn't show traffic rates.

It's the same with metabolic pathways; when you're looking at these diagrams, you have no idea how efficient a pathway is in converting compound A into compound B. But if you have a flux map, which is a map of the rates of individual reactions, it's like having a traffic map. And that will tell you whether a particular pathway plays an important role for converting a precursor to a product in a particular organism or whether you should try a different pathway because a particular reaction is too slow. You can get that kind of information by doing C-13 flux analysis and by using other stable isotopic tracers. This is now one of the tools of metabolic engineering. So these papers by Wiechert *et al.* were very important contributions to the journal and to the field, and there are many papers in that area that we've published since.

SW: Was it difficult to convince Wiechert and his colleagues that they should publish such important work in such a relatively new journal?

Not really, because he's one of the people who fit very naturally in the community of metabolic engineering and also in the constituency of the audience of the journal. He's one of the natural readers and contributors. In general, the large majority of the papers we publish are submitted unsolicited.

SW: Have there been specific developments in the fields served by your journal that may have contributed?

I would think the current interest in renewable fuels is a major external factor, which brings metabolic engineering to the forefront. Metabolic engineering is the enabling technology for the production of these fuels from renewable resources. Another one is synthetic biology, which is simply a method for making synthetic DNA for constructing synthetic pathways in microbes. As such, the main application of synthetic biology is in modifying and optimizing metabolic pathways, which is the goal of metabolic

engineering. A lot of metabolic engineers nowadays use genes that have been made synthetically.

People often confuse synthetic biology and metabolic engineering. The best way to view these two areas is that synthetic biology provides synthetic DNA for pathway construction; metabolic engineering provides the strategic directions for pathway modification and gene targeting by analyzing and assessing such pathways. It is important to remember that metabolic engineering preceded synthetic biology by two decades in the context of pathway modulation for product synthesis. The ideas of cell factories and microbes as product formers have been around a long time before the ability to synthesize DNA became a mail-order laboratory function.

SW: How do you see the field of metabolic engineering evolving in the next few years?

First of all, I think metabolic engineering will continue to get more and more recognition. A lot of life scientists are becoming more aware of the field and biofuels is a good catalyst for that, but only one of many. In just 15 years this field has had some tremendous successes: microbes have been engineered to make fuels, amino acids, biopolymers, pharmaceuticals, different types of chemicals. So metabolic engineering does not go unnoticed any longer. People pay attention.

"… there's a lot of interest in using microbes for utilization of renewable resources and making fuels and chemicals from them."

As for where it's likely to go from here, I think the prospects are very bright. The production of renewable fuels from renewable resources is very promising indeed despite current oil price gyrations, and microorganisms are very well suited to do this kind of work and to compete very well with chemical methods. So this area will be growing by leaps and bounds. I have been getting lot of telephone calls about using microbes to convert biomass into major chemical products. That has a bright future.

Yet another big area where people are just scratching the surface is in medical applications of metabolic engineering. Diabetes and obesity are essentially metabolic diseases, and so mapping the flux landscape in these diseases will be very important to do if we're to have hope of understanding them.

SW: What do you mean by the flux landscape?

If you compare, for example, the flux maps of liver cells from a normal individual to liver cells from a diabetic, you may find different patterns of glycolysis, glycogen production, respiration, etc. And, if they're different, are all diabetics different in the same way?

Even more important, you can consider cancer a metabolic disease. If you go back to Otto Warburg's work at the beginning of the 20th century, he noticed that cancer cells grow faster than other cells in the organism and, if they're growing faster, they must be consuming a lot of glucose and oxygen—their metabolism must be different. He made some very beautiful observations along these lines.

In the 1980s and 1990s, with the avalanche of research on oncogenes, signaling cascades, etc., we got totally away from the metabolism of the cancer cells. Now we're having a return to the concept of cancer as a metabolic disease. If we take tumor cells and study them with the methods of metabolic engineering, we can discover significant variations compared to the metabolism of normal cells. This might give us clues to what may be going wrong in a cancer cell vs. a normal cell, and this kind of analysis is now allowed by the very high resolution with which we can dissect the fluxes and the internal metabolism of these cells, again using isotopic tracers.

You can see the importance of studying the flux landscape when people come to suspect that a particular metabolite may be an important precursor in the production of a useful product. Say someone hypothesizes that some pathway is ATP limited, for example. To test this hypothesis one may do an experiment aiming to increase the supply of ATP followed by a measurement, typically of ATP concentration, to determine whether the experiment succeeded or not. What is often found is that the level of metabolite is virtually unchanged, because the organism compensated with a lot of other mechanisms. The level of ATP may have stayed unchanged, however, its rate of supply may have changed by an order of magnitude. Only flux measurements can assess accurately the success or failure of these hypotheses.

The point is that just knowing the level of the metabolite tells you absolutely nothing about the rate at which the metabolite is formed or depleted. That is such a simple point, but you'll see this misinterpretation frequently. People look at the level of ATP and they see that it's constant and so they say, "OK, my efforts failed." Again, here is when flux analysis is critical and comes into the limelight.

SW: What role do you see for your journal in the coming years?

I'd like it to become the premier place for publishing the kind of work where people modulate genes cells and then do the difficult job of describing the result of that genetic modification. While it's nice to be driven by a hypothesis or by a good model, in many cases that will not be possible. So, besides the rational approaches of metabolic engineering we would also like to cover combinatorial methods that have been shown to have a lot of potential.

I'd also like *Metabolic Engineering* to rise up in the impact factor game. Right now the field of biotechnology is in a not very pleasant situation: you have the very high-impact journals and then nothing until you reach an impact factor of 2-3. This is really not good, as it undermines the importance of many journals and concentrates attention on the top few. So I'd like *Metabolic Engineering* to be the high-tier journal that attracts the best work out there.

SW: What plans, innovations, or improvements would you like to implement for the journal in the coming years?

I do have lots of plans. What I don't have is the time to implement them. That's my problem—too many things on my plate. I certainly would like to pay more attention to getting good reviews in the journal, organizing some special issues in critical areas for metabolic engineering. There is one in the field of biofuels that will be coming out soon, for example. That's one area I think we should try to cover very well.

But it's important to keep in mind that this journal, like many others, is basically based on volunteers. We don't have the staff to assign them functions to do special reporting, to write special features, all the things you see in the top journals. Those journals have large staffs that they can use for this purpose. We have to do the best we can with volunteers.

SW: What would you like to convey to the general public about the work of *Metabolic Engineering*?

To pay more attention to the field of metabolic engineering. This is the field that codifies the enabling technology for using the tremendous power of biology as an alternative to chemistry. In essence, metabolic engineering is a new type of organic chemistry. Instead of synthesizing things in test tubes, we synthesize them inside microorganisms. We use them as little chemical factories, and the potential for very efficient and very clean processes is just enormous. We are only scratching the surface in this regard.

Metabolic Engineering
Greg Stephanopoulos, Editor
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PDF

back to top

Journal Interviews : 2009 : Metabolic Engineering

Scientific Home | About Scientific | Site Search | Site Map