

The model of intelligence

An interview with Dr. Chris Penland of Novartis



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— Chris Penland, Senior Expert Modeler at Novartis

Introduction

After completing his doctorate in biomedical engineering in 2002, Dr. Chris Penland, who also holds two degrees in nuclear engineering, led a number of modelling initiatives. He leverages the considerable experience that he gained throughout his studies to help improve pharmaceutical decision-making in rational drug design, dose guidance, efficacy and safety trade-offs, and appropriate treatment regimens.

In 2008, Chris started work with leading healthcare company Novartis as a senior expert modeler in the company's global modelling and simulation group. The team serves the entire Novartis organization, including pharma development, research, generics, OTC, and animal care. Chris' responsibilities include supporting certain projects with integrated modelling of disease physiology, pharmacokinetics, pharmacodynamics, and clinical outcomes. He is also the group lead for modelling mechanisms of drug induced cardiac and liver toxicity.

Here, Chris talks about his career and current work, as well as how he uses solutions like PharmaPendium and ScienceDirect® for his research.

Interview

For my doctorate, I focused on the computational simulation of cardiovascular electrophysiology; my objective was to better understand how characteristics from the subcellular to the whole organ integrate to form the preconditions of arrhythmia and how can we develop improved therapeutics and devices for abnormal heart rhythms. I decided to specialize in cardiovascular work because it is an area that affects so many people: a huge number of Americans but also a growing worldwide population.

At Novartis, we are deeply committed to the optimal development and use of drugs. Our global approach is to integrate the principles of biology, pharmacology, and statistics to explain and predict the quantitative consequences of decisions through the application of mathematical models.

As a group, we construct models of dose exposure and mechanisms of action, helping teams to plan and analyze trials. We are also involved in making recommendations and supporting multifactorial decisions for actual doses, based on therapeutic window, risk benefit analyses and other criteria.

Alongside the variety of information generated by the program through internal trials, we also work on metamodeling, drawing on, for instance, published trials of competitor compounds from a class or observational studies on the natural history of a disease and then constructing an overall model of disease progression and the various therapeutics involved.

This is increasingly important for evidence-based medicine: when you are taking a medicine forward attempting to gain approval, acceptance and reimbursement. Where possible, we work with colleagues in Novartis' Health Economics & Outcomes Research group to show that a new therapy represents an improvement over the current care available and our competitors' products currently in development.

In cases where there is a very strong medical endpoint, you have to demonstrate an adequate effect on that endpoint. Take the example of anti-diabetic drugs; their overarching purpose is to improve clinical outcomes by controlling blood sugar levels, measured by a reduction in the marker HbA_{1c}, therefore regardless of mechanism, an effective therapy must lower HbA_{1c}. In reality, there are a number of compounds out there that offer a rapid reduction in HbA_{1c}, but do not lead to a greater over-all reduction compared to slower-acting compounds. This is important when we start to compare trials of various lengths against one another.

Information in a short trial may favor the faster acting drugs, but in actual clinical practice — when people are on medication for six, nine or 12 months (or even years) — the overall benefit of the faster drug may not actually be any greater. So, when we compare our compound, we need to understand the time dynamics of the onset of the effect in conjunction with the extent of the effect in the future.

In diseases that do not have a strong marker correlated to actual clinical success, we try to capture this uncertainty in our quantitative models to help the teams as much as possible. There are many things that still have to be determined through the pivotal trials.

Obesity, hyperlipidemia, and metabolic dysfunction continue to be growing health concerns globally so we are looking in particular at ways to address this through novel mechanisms and improved understanding of the disease, efforts in which modeling and simulation can play an important role.

Rather than trying to get rid of fatty acids after they have been absorbed — or preventing them from doing damage once they have been absorbed — why not prevent their absorption in the first place? To be fair, this has been tried before and there are agents out there that are not very tolerable making the use of such medications a fine balance. Our group focuses on integrative, quantitative methods for getting the right dose to balance efficacy and tolerability in particular patient populations.

I'm also particularly interested in targets for improving HDL cholesterol and whether or not they will prove to be a meaningful therapy.

The big surprise here was torcetrapib by Pfizer. It did what it was supposed to do, which is raise HDL however, the link between HDL and clinical improvement in the patient — prolonging their life, preventing them from ending up in a hospital with an infarction or a stroke — is not so clear.

These compounds worked biochemically, but the biochemical to clinical linkage was insufficiently strong or not completely understood.

Symptomatic relief is very important and worthwhile in many diseases but, where possible, my goal is to work on compounds that delay disease progression and improve the survival curve.

In all of these areas however our main challenge is information; being able to efficiently identify, filter, and integrate internal and external data. We have to keep on top of everything that is happening competitively and in the literature.

We have the human resources to build and analyze models. Where we run into a bottleneck is in efficiently identifying and sifting through large amounts of data to determine what can and should go into the models to address the specific challenges the programs and organization faces.

We have a dedicated group of programmers, whose job it is to collect and format data from Novartis' clinical trials, forming these into a dataset that is ready to be modelled. Even under standardized data management in a single organization, these trials are not exactly the same in terms of their data framework. Therefore, our programmers have to resolve these issues on a trial-by-trial basis, both within Novartis and within the industry.

Of course, many useful trials are over 10 years old; these will never be translated to a new format without significant investment. So, for the foreseeable future, integration of these types of trials will be an on-going issue.

Another problem is filtering information. If I search for, say, metformin — an extremely common diabetes medication — I am overwhelmed by the search results. Filtering that data down to the bellwether compounds or manuscripts without accidentally throwing out important but less publicized findings can be time consuming.

It's a very different problem from keeping abreast of the small amount of literature that is emerging on brand new compounds or new mechanisms. It needs a research and discovery mentality. One big step forward that the group from Elsevier took recently is in enabling us to scan through pictures of papers.

Previously, we'd have to go through the full texts to see if the paper had the information we were looking for and sometimes we would find that a particular article did not have new information, but rather cited another original source. Now I no longer have to read the full text: I can scan through the figures and tables to triage articles and find the information that I need.

There are some very interesting semantic searching and text processing developments in progress too, which will be beneficial for searching information: rather than simply looking for papers which contain search terms, semantic search engines will look for matching terms with the same contextual meaning. This is making the searching process much more intelligent.

A number of companies are also developing search engines that will trawl the information that an organization has access to. Thus, the results will differ whether you are, say, an academic, a small firm, or a large pharmaceutical company that has a broad range of subscription licenses.

A major boon for us will be the ability to store information in federated databases, or in search aggregator interfaces meaning I don't have to spread my time over different interfaces. Without this, information

could be hidden because it was stored in very different ways. In some senses it is a bit like PharmaPendium; you're drawing from a variety of sources with a common search term, and within the same interface.

In all, I probably devote around two hours per week to nothing but searching. I have a short list of bookmarks to internal Intranet sites and external sites. I use bibliographic citation manager software and I have a diary document that I cut and paste things into, helping me to keep track of the searching process. Novartis intranet has a one-stop shop for all of our external databases, e-journals and subscriptions like PharmaPendium, Pink Sheet (from the FDA) and Thomson Reuters.

Elsevier and Nature Publishing Group are the two companies that I depend on most. I think that, in terms of usability and dynamic presentation of information, Elsevier is way ahead in providing more intelligent information. When I look at your website, I am always amazed that there are so many more applications than the ones that I use. You provide an access point to valuable information. Over the past three to five years, Elsevier has provided more and more tools to make the information 'come alive' and be more dynamic. Even if you did not have any of your own content — just an application that drew from everyone else's — it would still be extremely useful. The fact that you also have their own content makes their service even more valuable.

Elsevier offers a huge amount of content, and you have some very good applications for dealing with it. They do not have to go 'door-to-door' to other publishers. I think this has given you a real competitive edge.

In particular, I use PharmaPendium to search for health authority review materials, labelling packages, adverse events and pharmacokinetic data. It is very nice when you find citations or references from your search. As modelers we are always looking for data and parameters about phenomena in our systems, and with PharmaPendium, I get information about how it was measured, and a click will show what source document it came from — all very important for building robust, well-founded models.

This is very useful, particularly when dealing with regulatory submission packages for the FDA and the European medicines agency, to see the information on which their decisions were made. Of course, because it offers such rich data, it can take time for reports and newer compounds to be added to the PharmaPendium database. Thus, there is an issue of timeliness. But I am not sure that can be helped — at least, without an army of content curators.

I also use ScienceDirect for literature searches, setting alerts and image searching. And I have to say, I cannot really think of a weak feature. Even on its worst day, ScienceDirect is better than everything else I've used.

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