



# Under the hood of *DNA*

by Harold  
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The human genome has been fully mapped, but working with it is still a daunting task. **Mads Kaern** is devoted to finding out how all the genetic components interact and respond as a system.

Here is possibly the most difficult, inefficient and just plain bone-headed way to learn how a modern car works: take out one part at a time, and see what happens.

Yet according to Mads Kaern, this is more or less how genetics research—by necessity—used to be done. “In the past, we analyzed genes by removing them, and then seeing what the effect was,” he explains. “That’s a bit like trying to understand how a car works by pulling out a cable.”

The approach doesn’t work for cars, because they comprise many complex systems that communicate with each other and modify each other’s behaviour, based on changing conditions. Information from a sensor in a labouring engine causes the automatic transmission to downshift on a hill; a signal from the accelerator pedal tells the fuel injectors to go faster. To really understand that shiny beauty in the driveway, you have to know how all those components interact and respond as a system when the car is in motion.

That’s roughly what professor Kaern is trying to do with genes.

Somewhat like the parts in a car, interacting components within our cells control how our genes operate. These “gene regulatory networks” consist of proteins, molecules of the chemical RNA and even other genes. In response to various kinds of stimuli, the networks generate signals that determine how (or if) a particular gene will “express” itself—whether it will trigger the creation of a protein or an enzyme, or if it will signal another gene to act, or even do nothing at all.

And the outcome isn’t trivial. The way our genes express themselves controls to a great extent whether we’re healthy or sick. The more we understand how gene regulatory networks operate, the more control we’ll have over a multitude of diseases.

Kaern focuses on understanding the principles that govern the design of these networks. But working with the human genome, mapped as it may be, is still a very daunting task. “It’s very difficult to analyze these systems in a human setting,” Kaern explains. “We haven’t identified all the genes yet, and we haven’t identified all the factors that contribute to these systems.”

To simplify the problem, he’s currently working with yeast—a single-celled organism with a relatively small genome. And he’s using the emerging tools of synthetic biology to create

simple artificial regulatory networks he can introduce into yeast cells, and then observe the results. “High-throughput” technologies enable him to create, test, and analyze thousands of variations at a time.

But—of course—there’s a further complication. To return to the auto analogy: car components can be relied on to work the same way over and over again (until they wear out). In the language of statistical science, their behaviour is deterministic. Genes are less predictable. Even if the signals from the regulatory networks are the same, there isn’t a certainty that a given gene in cell A will respond the same way as its counterpart in cell B—there’s only a probability.

To take this into account, Kaern uses sophisticated statistical approaches developed for the study of physics—a discipline in which he is cross-appointed at the University of Ottawa.

The goal, of course, is not simply to understand regulatory networks. “We want to be able to modify these networks so they can respond to the specific signals we choose, and trigger the behaviours we want,” Kaern explains. “And we want to be able to design new regulatory systems too.”

Some of the early applications he foresees include engineering specialized organisms to create biofuels out of different kinds of waste products. But the holy grail is human application. “If you could design and deliver the appropriate regulatory network to cells, you could trigger drug production right inside cancerous cells,” he says.

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– Mads Kaern

Delivering these custom-designed networks will be a big challenge. Gene therapy is the enabling technology that will make it possible, yet barriers in that field are still formidable. Nevertheless, Mads Kaern is confident that in perhaps a decade, when his research is ready for human application, gene therapy will be ready too.

And that’s going to mean that many of us will eventually be able to get the genetic overhauls we need to keep us purring like a Rolls along the highway of life. **RP**