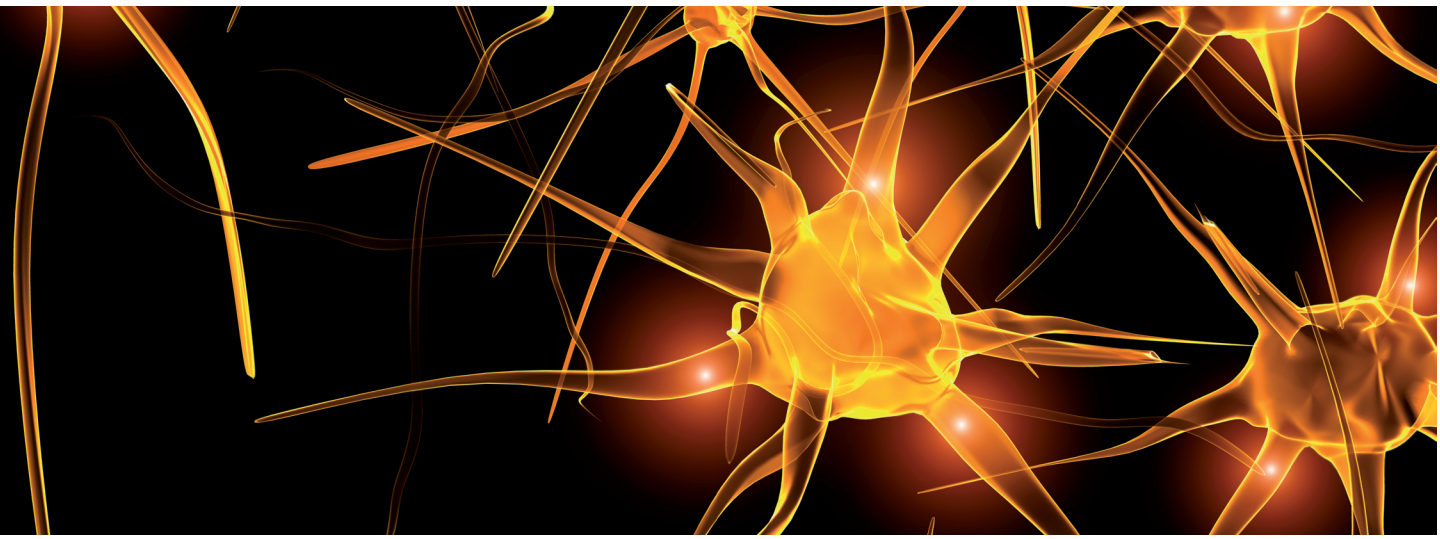
Expanding the understanding of the nervous system requires sophisticated techniques capable of integrating several sources of experimental data. Combining biophysical simulation with parameter search allows researchers to study the relationship between normal function and diseased function in conditions like epilepsy and chronic pain, says **Erik Fransén**

Modelling clues to understand disease



Excess production of nerve impulses is known to be one of the primary causes of the symptoms of epilepsy, yet there are many underlying factors behind the condition, including changes in ion channels, signals within the cell and cellular networks. Studying epilepsy requires correspondingly sophisticated techniques, an area being addressed by Erik Fransén, a specialist in computational biology at the Swedish Royal Institute of Technology.

"The main goal of my group is to study normal and dysfunctional mechanisms of the nervous system; we're really focused on biological or medical questions. In this particular project we're using a combination of biophysical computer simulations and numerical search for model parameters. We're using a parameter search technique called direct search to find how the model best agrees with experimental data," he says. This methodology is being used to look at both epilepsy and chronic pain. "Important parameters in epilepsy models include the properties of ion channels, the concentration of calcium inside neurons or the efficacy of synaptic connections. A typical parameter would be the maximum current or density of an ion channel," continues Fransén. "An ion channel is a specialised protein that sits in the membrane of a neuron, it can also be found in other excitable tissue of the body. Ions like sodium or potassium can pass in or out of the neuron via these specialised pores, most of them open and close for particular reasons."

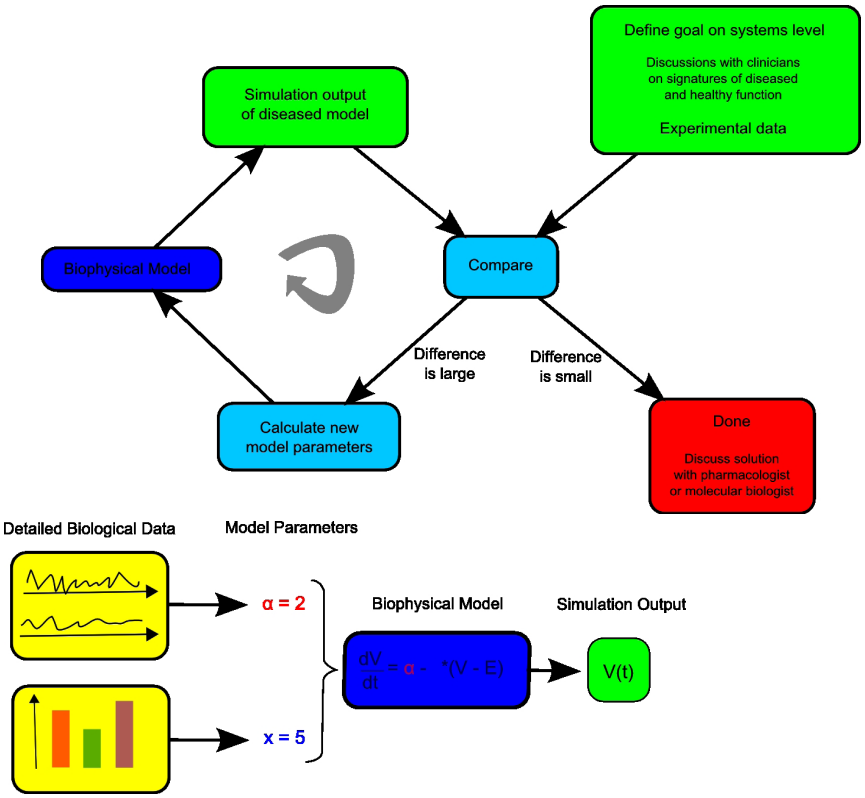
Making models of neurons

This action of opening and closing is a feature that Fransén is keen to capture accurately in the biophysical models. Changing the electrical voltage over the membrane of a cell can either open or close an ion channel, and thereby allow ions to go in and out. "The ions themselves change the electrical voltage, and the nerve impulse itself is an electrical event, so the nerve impulse is produced by the coordinated action of different ion channels," explains Fransén. These ion channel models are based on experimental work. "Equations on how they open or close are derived experimentally and we can then replicate the opening and closing of ion channels on the computer.

The result will look very similar to the experimental record. In this process, we will use data on a small level, ion channels for instance, but the output will be the output of a whole neuron or the activity of a system of interconnected neurons. By this, we are able to bridge levels from small to large," says Fransén. "The function we get can thereby be based on a large amount of separate sets of experimental data."

Parameter search strategies

The main focus of this work is on solving medical problems. The group is looking at both healthy and diseased states, and using parameter search optimisation to understand the relationship between the



two; the majority of the data is from animal models of epilepsy, but material from human patients is also being used. "In our modelling we use data from a human epilepsy patient; there's a single mutation in one gene – coding for an ion potassium channel, the A-type potassium channel. This was cloned, and researchers characterised the biophysics, then we included that biophysical information in our model. So we can say that this is a model of that particular person's potassium channel," says Fransén.

"We have shown that replacing the A-type potassium channel with this channel gives a neuron pathological characteristics." The group's current work centres on studying how changing properties of ion channels can make that neuron function normally.

"With our method, we use the search algorithm to find the changes needed to change the properties of the neuron from those showing the signatures of disease to those of the healthy cell.

With more information from clinicians about what aspects of malfunction to correct, the more precise our search will be. Making the parameter search algorithm identify properties of ion channels to make the neuron behave in a more healthy way means we get solutions at the molecular level, the ion channel, which are of great interest to pharmaceutical companies," continues Fransén. "Ion channels constitute a particular class of target for the pharmaceutical industry."

'In silico' target design

Pharmaceutical companies commonly use a target approach to development, where for instance a receptor at the surface of a cell is identified and molecules that activate or block the receptor are developed. This approach is known to be difficult, as substances with promising effects on cells cultured in a dish turn out not to have a sufficient effect on the symptoms of the patient. "Going from the doctors list of clinical symptoms that need treatment to then selecting a target that a drug should act on is very difficult," says Fransén.

The process from initiation of the search for targets to clinical trials is very time consuming and costly; by contrast as computer simulations are far less expensive than experiments, Fransén says the search process can be repeated many times and many combinations tried.

This work is of great interest to the pharmaceutical sector, and biophysical modelling could be used to address a range of biological and medical problems; Fransén is already collaborating closely with AstraZeneca in a project on peripheral chronic pain. "Pain is increasing in Western societies but it is not really understood why.

We use the same methodology and the same strategy – it is very clear that pharmaceutical companies want to develop drugs to address pain symptoms," he says. "Pain is very complex and you don't want treatment to cause unwanted side-effects. Unless you understand the problem you won't be able to fix it in the most effective way."

At a glance

Project Information

Project Title:
In silico target design
Biomolecular target design using computational modeling

Project Objective:
In this project, we develop a computational search method to design ion channels so that they can achieve optimal physiological/ terapeutical effect on cell or network function. The project currently evaluates direct search strategies to find optimal characteristics. In each cycle of the procedure, new channel parameters are set, next biophysical simulations include the channel in the cells of the network/system at study. From the simulations, resulting physiological function is measured/evaluated. Based on this evaluation, new parameters are computed using the search method.

Project Duration and Timing:
01/01/08 – 12/31/10
negotiation in progress

Project Funding:
Swedish VR 621-2007-4223
AstraZeneca

Erik Fransén

Erik Fransén is associate professor in computer science at the School of Computer Science and Communication at the Royal Institute of Technology, Stockholm, Sweden.
He was a post doctoral fellow at the Department of Psychology at Harvard University during 1997-1998.
He is presently school director of doctoral studies, vice head of the department of Computational Biology and director of the masters programme Computational and Systems Biology.

Contact

Main contact name:
Erik Fransén

Tel: +46-8-7906902
Email: erikf@csc.kth.se
Web: http://www.csc.kth.se/~erikf