Eighteenth century minister's mathematical theorem helps scientists map out cell signalling pathways

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(PhysOrg.com) -- Researchers at the University of Glasgow have successfully exploited statistical inference and mathematical modelling to discover how cells communicate.

In a world-first, a multidisciplinary team of statisticians and computer scientists led by Prof Mark Girolami; molecular pharmacologists led by Prof Miles Houslay and Prof Graeme Milligan; together with cancer biologists led by Prof Walter Kolch, used Bayesian-inference-based modelling to establish which pathway was utilised in a particular cell signalling event. (Bayesian inference is a statistical tool which uses evidence to update existing knowledge of a hypothesis in order to develop it further and is named after Bayes' theorem, created by the Reverend Thomas Bayes (c1702-1761).)

The method, which is based on the theorem of 18th century minister the Reverend Thomas Bayes, takes account of evidence to refine a hypothesis and offers the possibility of increasing our understanding of cell signalling pathways and how drugs might alter them to prevent disease.

Cells communicate with each other by sending messages through proteins which bind to each other and result in a series of chemical reactions cascading down through the cell - a pathway - to produce a change.

Errors in this signalling can often result in disease - for example when cells do not follow instructions to die they continue to divide leading to the growth of tumours.

Professor Mark Girolami, professor of computing and inferential science, who led the project, said: “There are a number of pathways in which cells can communicate but knowing which route is taken is very difficult. Conducting experiments to find out is impractical because of the time it would take, but mathematical modelling can help narrow down the possible routes.

“Being able to know the structure of these pathways and how different proteins are recruited in the process of signalling could pave the way for drugs which could trigger or suppress these reactions to treat disease.”

In their study, the Glasgow scientists investigated the signalling pathways used by Epidermal Growth Factor (EGF), a protein which stimulates cell growth.

Once the EGF protein has attached itself to a cell, there are a number of pathways through which its signal can travel to the cell’s nucleus.

“Using Bayesian-inference-based modelling we were able to narrow down the possible pathways to four and predict which is the most likely. These pathways could then be tested experimentally,” said Prof Girolami.

The experiments revealed that the predicted pathway was indeed the pathway used to transmit the EGF signal; furthermore, it was discovered there were particular proteins involved in the pathway which were completely unexpected.

Prof Girolami added: “Bayesian-inference modelling provides a rational

and systematic way of exploring a hypothesis. It can be applied in many fields, for instance, we're even working with geotechnical and petroleum engineers to establish which boreholes are likely to yield the most oil."

The research, which took four years, has resulted in a huge number of enquiries from scientists from around the world.

The paper authored by Prof Walter Kolch, formerly of the Division of Integrated Biology and now Director of Systems Biology Ireland and the Conway Institute, University College Dublin, was published as the cover story of the journal *Science Signalling*.

Provided by University of Glasgow