MATHEMATICAL MODELLING

for better diagnosis and treatment of eczema

Dr Reiko Tanaka and **Professor Alan Irvine** describe a mathematical modelling approach to the study of eczema, which has been developed at the Department of Bioengineering, Imperial College London, in collaboration with Trinity College Dublin and the Japanese research institute RIKEN.

Given the wide variety of the disease severity and symptoms of eczema, which differ from individual to individual, patients may benefit from personalised treatments tailored to their own specific needs. Eczema symptoms vary greatly depending on each patient's genetics, environmental factors and disease history.

We recently applied a novel ***mathematical modelling approach*** to understand the complex interactions among these factors that lead to different manifestations of eczema. This research is expected to help develop personalised treatments.

What is a mathematical modelling approach?

We examined data from approximately 500 previous clinical and experimental studies on eczema to develop a complex mathematical model that explains how the dynamic interactions between the skin barrier, the immune system, genetics and environmental factors can lead to disease over time. The mathematical model represents a virtual patient cohort in computers, where variation of the parameters characterises different patient cohorts. For example, patients with filaggrin mutation are described with a larger parameter for skin permeability, and those with a dysregulated innate immune system are described with a smaller parameter for immune responses. Computer simulation of the mathematical model for individual virtual patient cohorts can simulate and predict how eczema develops, and how it progresses to become chronic, and can be treated, over time. The mathematical modelling approach thus helps us better understand eczema, by providing us with the mechanistic explanation behind the clinical observations and predicting how changes to the system – for example, by treatments – will affect disease.

What did the mathematical models identify as a mechanism of eczema worsening?

The mathematical model could explain why some patients develop a more severe form of eczema than others, and suggested four types of patients with eczema, ranging from those with no active symptoms to those with severe disease.

The computer simulations of the mathematical model identified that repeated flare-ups of eczema may trigger an immune system overreaction in the body and, when triggered, this can't be reversed. If the immune activation is short-lived, the symptoms of disease will disappear when the immune response comes to an end naturally. But if the immune activation lasts too long, or happens too often, then the immune system becomes overwhelmed, and can't 'switch-off'. In this case, the symptoms of disease continue, often worsening with time. This creates a cycle where the threshold for triggering further flares becomes lower, the flare-ups are more severe, and the condition progresses to becoming long-term. The computer simulations also demonstrated that exposure to environmental stressors cause longer and stronger flares if patients have genetic predisposition for atopic eczema.

What did the mathematical models identify as a key to preventing eczema from becoming more severe?

The mathematical model analysis further suggested that the key to preventing eczema from becoming more severe is to prevent an immune system overreaction from being triggered. This explains how moisturising treatments may help to protect newborns from developing eczema, as shown in two recent clinical trials that demonstrated that babies who received moisturising treatments by emollients – which were applied directly to the skin to reduce water loss and cover it with a protective film – were less likely to develop eczema. By reducing water loss and creating a barrier, moisturising treatments break the itching and scratching cycle, and thus protect against skin damage, and subsequent immune activation. The mathematical model further demonstrated that moisturising treatments could help to prevent all newborns – not just those with genetic risk factors – from developing eczema.

What are the future steps for the mathematical models to help patients?

To make this mathematical modelling approach directly applicable to patients, more work needs to be done to verify the model results, using the patients' data on how the symptoms develop over time for different patient cohorts. We then hope to develop a model that can be tailored to each patient, based on the individual clinical data. This could enable doctors to tailor treatment to the specific needs of each patient, optimising its effectiveness, and lessening the severity and impact of the condition.

Using mathematical models to understand the underlying causes of diseases or conditions is called 'systems medicine' – an interdisciplinary research field that investigates disease mechanisms. It is a collaborative endeavour between clinicians, mathematicians, biologists and engineers to understand the complex disease mechanisms, identify the vulnerable patient cohorts who would benefit from preventive treatments, and identify and test better diagnosis and treatments.