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SARCHI project - Mechanistic modelling of health and epidemiology

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The currently used mathematical models for medical treatment at the individual or population level are largely phenomenological and have limited quantitative predictive power. It is usually not possible to predict the effect of an intervention in a specific process or to predict the effect of a pharmaceutical drug since the step or enzyme on which the intervention/drug works is not explicit in the model.

Taking HIV pathogenesis as an example, the immune system response, vaccine exposure, and drug regimen all affect viral replication and onward transmission, which may be a single parameter in a model. Or in higher-level scenarios of epidemiological intervention, condom distribution, behavioural messaging, and vaccines may all be affecting a single transmissibility parameter.

In 2013 Prof J. Snoep took up the SACEMA SARCHI Chair in mechanistic modelling of health and epidemiology. The task of the chair is to provide a mechanistic modelling approach with more predictive strength to pharmaceutical drug and intervention steps for individual and public health compared to current models. In this contribution an overview of the project is given and some of the work performed in the first year is highlighted.

Focus of the SARCHI project

In the current and foreseeable era the hyper-endemic infectious diseases, in particular HIV, TB, malaria and their associated complications, are the defining challenges to planning and running the regional health system. This raises questions on many levels; drug targets, cellular mechanisms, clinical process, and epidemiological trajectory. SACEMA's and the SARCHI Chair's mandate is to grow the South African community of practitioners of formal quantitative methods who can work to support policy formation and evaluation by providing data and model driven analysis to ultimately underpin national scenario modelling for infectious disease epidemiology.

The approach to model mechanistically from the biochemical level up to epidemiology is unique in South Africa and state of the art internationally. The work of the chair will focus on three areas:

1) a fundamental research component for a mathematical modelling framework to bridge hierarchical scales from biochemical reaction steps to population dynamics;
2) a service component for a web-enhanced, mathematical model database of biological systems; and
3) an application component in which 1) and 2) are applied to a selection of diseases that are important in the South African context, initially HIV/AIDS, TB, malaria and diabetes type II.

The research focus of the SARCHI Chair is perfectly integrated with the current research at SACEMA, where a diverse range of mathematical and statistical models are being applied to multiple levels in order to shed light on questions ranging from basic disease processes to optimisation of interventions. The SARCHI Chair will consolidate the SACEMA activities by strengthening the detailed biological content of whole body disease and epidemiological models. More specifically, the SARCHI research plan links to SACEMA efforts on three levels: 1) the formal underpinning of the multi-levelled modelling work; 2) its systematic alignment to data; and 3) the quality and availability of relevant tools to enable comparative deployment by the wider research community, in particular in pursuit of policy scenario modelling.

Team of researchers involved

In the first year of the project focus has been on establishing a research group and extend the scope of existing projects to the level of whole body disease states.

The SARCHI Chair will develop the methodology to construct mechanistic models for HIV/AIDS, TB, malaria and diabetes by combining existing (and new) models, within a hierarchical mathematical framework that will be developed within the project. A framework for constraint based hierarchical modelling will be applied. This framework will ultimately integrate detailed biochemical knowledge of disease with the higher level of population dynamics, leading to both qualitative and quantitative interpretations and predictions of the effect of specific interventions; at the whole body level for individual health and at the population level for public health. The research undertaken by the chair will significantly strengthen the mandate of SACEMA by merging the biostatistics and population dynamics approaches with a strong programme at the biological level through experimental, software

engineering, and mathematical modelling components. By using more mechanistic models with a stronger biological content, the predictive power of these models will be greater than that of the currently used phenomenological models. The focus point for application of the mechanistic models is to underpin national scenario modelling for infectious disease epidemiology.

The hierarchical modelling frame work is being developed by D. Palm who is testing the method on detailed kinetic models that have been developed in our group for central carbon metabolism of the malaria parasite *Plasmodium falciparum*. G. Penkler, F. Brand, and W. Adams have measured kinetics of all enzymes in the glycolytic pathways and constructed a mathematical model for glucose metabolism. This model was tested on isolated parasites and could predict glucose metabolism well. The model was subsequently merged with a detailed model for the red blood cell by F. du Toit and again tested in its predictive power of glucose metabolism in infected red blood cells during the life stages of the parasite. M. Meiring, F. du Toit and A. Leussa Nyango-Nkeh are extending this model to include parasite growth and reinvasion in red blood cell cultures. This work will be extended to whole body modelling of glucose metabolism in malaria patients. Currently N. Walters is starting experimental work in an animal model in collaboration with L. Wiesner at Grooteschuur hospital. The overarching aim of the malaria project is to understand the nature of hypoglycaemia and lactic acidosis observed in severe malaria cases at a whole body level. It is not possible to simulate a whole body model at the level of detail of individual enzyme catalysed reactions, but the hierarchical modelling framework will make it possible to predict the effect of partial inhibition of an enzyme in the parasite at the whole body glucose metabolism level.

For the HIV part of the SARCHI project we appointed J. van Zyl and A. de la Harpe to make comparative analyses of existing mathematical models for HIV at the whole body level and epidemiology, respectively. These studies involve coding and curation of these models, making a functional comparative analysis and adding the models to the model database. For the service component J. Eicher was appointed as coder for the JWS Online model database and simulation tool. D. van Niekerk was appointed in the Biochemistry department as partner in the SARCHI project and to take over the lecturing load of Snoep.

In 2014 we will start clinical trials on metabolic side effects of ART treatment of HIV patients in collaboration with F. Essop from the Physiology department at Stellenbosch University and the ANOVA team.

Jacky Snoep - Professor in the Biochemistry Department at Stellenbosch University (SU). Research interests: to get a quantitative understanding of physiological processes using a multidisciplinary approach of experimentation, modelling and theoretical methods. He was awarded a SARCHI research position to develop mechanistic models for disease states and epidemiology for which he works both at SACEMA and at SU. jls@sun.ac.za