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Title: Mathematical models and hepatology; oil and vinegar?

Mathematical models are increasingly being used in medicine to study physiological, pathophysiological and therapeutic pathways[1–3]. In hepatology, mathematical abstractions have been beneficial to predict the viral load of hepatitis C following treatment [4], outcome after acetaminophen overdose[5], or to quantify porto-systemic shunting and inter-organ ammonia metabolism at different stages of cirrhosis[6]. However, in many medical fields (including hepatology), there is much resistance to include theoretical models in their traditional tool set and furthermore a lack of confidence in the generated theoretical results. One obvious hindrance that prevents the expansion of mathematics in medicine is the difficulty to comprehend the methods and results, especially when described with technical terminology. However, even when results are presented in a clear comprehensible way, a suspicion remains regarding the validity of the model, and therefore the simulation-generated results and conclusions are mistrusted. This uncertainty may be further aggravated by the fact that although it is possible to appreciate the limitations of an experimental biological setting, understanding the limitations of a mathematical model is extremely difficult, even for mathematicians. Validating model assumptions and results is not straightforward [3]. In many cases, different assumptions (eg. number of transporters, concentration of enzymes, etc) could produce similar outcomes, and so attempting to validate a model by simply displaying concurrence between simulations and experimental data is not adequate. A more convincing way would be to use the model to formulate correct and surprising predictions. However, this is not always truly possible. So, with all this in mind, how can we increase the confidence in mathematical approaches? The key is to better understand what type of answer can be extracted from models and to recognize that a good fit between model simulations and experimental data is not necessarily the ultimate goal. Misfits can equally lead to noteworthy results, helping to discard competing scenarios or point to a missing component.

In this issue, Ghallab et al. provide an excellent example of how a misfit can provide new and exciting insights regarding the underlying mechanisms of hyperammonemia in acute liver failure. Here, the authors reinvestigated the results of their previous published mathematical

model of hepatic ammonia metabolism in mice following CCl_4 injection, and tried to understand why some of the predictions were significantly higher than experimental values [7]. At first, the authors believed the discrepancy was due to the calibration of the model. However, refining the estimation of parameters by including changes in the concentration of enzymes over time did not eliminate the discrepancy. Subsequently, the authors developed a hypothesis stating their initial model lacked a component; in other words, that a novel and unidentified mechanism should detoxify ammonia in addition to urea production and glutamine synthesis. After careful analysis of plasma components, the missing element was proposed to be glutamate dehydrogenase (GDH), a reversible enzyme that converts glutamate to α-ketoglutarate and ammonia. The rational was that in acute liver failure, GDH is released from necrotic hepatocytes in the extracellular fluid where high ammonia concentrations would favor the synthesis of glutamate from α-ketoglutarate. And indeed injecting GDH, α-ketoglutarate and NADPH in mice 24h after injection of CCl_4 rapidly decreased the blood concentration of ammonia. This hypothesis was further tested theoretically by inserting GDH into the mathematical model (one of the great advantages of mathematical models is that a new hypothesis can be tested rapidly). In turn, including GDH improved the fit with the data, which supported the hypothesis. This paper represents therefore a successful example of hypothesis driven by a mathematical model (model guided experimentation). The model helped identify and test a quantitatively important mechanism. The future lies ahead on whether GDH, α-ketoglutarate and NADPH can be used as a therapeutic strategy for the treatment of hyperammonemia in acute liver failure or if this cocktail is pertinent to patients with chronic liver disease where intra- and extra-hepatic shunting play a critical role. Unfortunately, the current model may not be able to answer these questions.

A dangerous temptation when employing mathematical models is attempting to answer questions that are beyond its limitations. A mathematical model is designed to answer a specific set of questions, and can rarely be extended. In the study by Ghallab et al., predicting the long lasting systemic effect of GDH (including α-ketoglutarate and NADPH) on blood ammonia levels would be unreliable without including the complex dynamics of glutamine, glutamate, ammonia (and α-ketoglutarate) in various organs.

With such potential, the question remains; how to promote the development of mathematical modeling in medicine? The strength of Ghallab's paper is the multiple (back and forth) exchanges between modeling and experimental results, which is probably not due to

chance. It is vital to expand mathematics in medicine and to develop close interdisciplinary collaborations. Medical researchers need to integrate mathematicians at the beginning of a study in order to measure the necessary parameters to calibrate a model. In turn, it is essential for mathematicians to closely discuss with researchers in order to identify the key components of the biological process, resolve which questions/model structures would help to discard the hypothesis, and discuss what model predictions would be clinically useful. One way to promote such interaction would be to physically incorporate mathematicians in laboratories and hospitals. Fruitful long term collaborations can help to understand the constraints and limitations involved in both mathematical modeling and experimental/clinical measurements. Such a simple change may lead the better insights in health and disease, and could play a powerful role in personalized medicine.

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Model of hepatic ammonia metabolism in mice after CCl$_4$ injection (based on current knowledge)

Inclusion of time-dependent enzyme concentrations in the model does not eliminate the discrepancy

Discrepancy between the model simulations and experimental data

New experiments

Explanation 1 : Issue with model calibration

Explanation 2 : The model misses an unrecognized but yet important mechanism of hepatic ammonia detoxification

Hypothesis: GDH released from necrotic hepatocytes detoxify ammonia

New experiments

Addition of this hypothesis to the model

Validation of hypothesis

New treatment for hyperammonemia in ALF?