A logical modelling approach to prepare and accelerate the design of ODE models: Application to bile acid metabolism

Lara Brueziere *(1), Eliott Tixier (1), Elise Roy (2), Arnaud Poret (3), Claudio Monteiro Sousa (1), Pietro Scalfaro (2), Jean-Pierre Boissel (1)
(1) Novadiscovery, Lyon, France, (2) ENYO Pharma SA, Lyon, France, (3) Laboratoire des Sciences du Numérique de Nantes, Nantes, France

BACKGROUND

The model of bile acids metabolism was developed in the context of a project for ENYO Pharma, where the aim was to model chronic hepatitis B virus and non-alcoholic steatohepatitis (NASH). One of the questions that the model had to answer was: what are the links between HBV replication and bile acids metabolism?

In order to answer this, a computational model of bile acids metabolism was built. However, developing a mechanistic physiology model based on Ordinary Differential Equations (ODEs) may prove time-consuming when studying complex biological systems. Additionally, most kinetic parameters involved in the biochemical equations of interest cannot be found in the literature.

This is why we introduce an intermediate step in our modeling process: the use of logical modeling approaches to prepare and accelerate the design of ODE models.

METHODS

The mechanistic bile acids metabolism model is based on curated knowledge extracted from white and grey scientific literature via the community-driven knowledge management platform (https://githealth.io). This literature review then leads to the construction of a logical graph (LG), which is a Boolean model enriched with fuzzy logic operators[1].

In the LG, each entity is represented by a node, and directed edges link the entity nodes to operator nodes. Fuzzy logic operators are the following:

- AND: $a \wedge b = a*b$
- OR: $a \vee b = a+b$
- NOT: $\neg b = 1\text{-}b$

On top of that, the edges from an operator node *j* to an entity node *i* are weighted by two values:

- The reactivity p_{ij} represents the rate of the associated reaction.
- The weakening q_{ij} represents the strength of the reaction, for example the difference between a partial agonist and a full agonist of the same reaction.

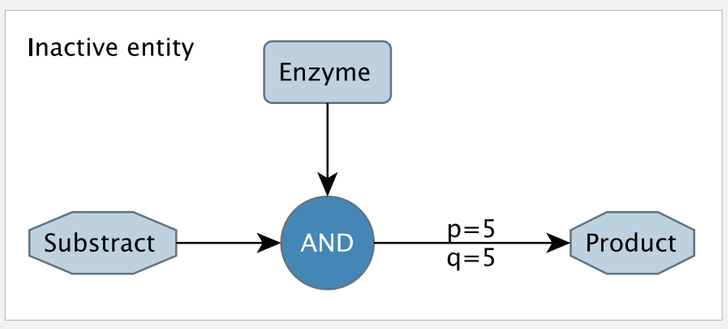

Figure 1: Representing a bioreaction in the LG.

The graph is then interpreted by an open-source software, logML. Each entity i has an initial condition defined in the graph, and at each iteration k, the value attributed to the entity i whose predecessor is the operator j is computed as follows:

$$enti(k) = (1 - pij\ ) * enti(k\text{-}1) + pij * qij * opj(k)$$

where $op_j(k)$ is the value computed from the operators nature and the values of its predecessors at iteration k. This then leads to qualitative outputs that estimate the variations over time of the quantity of each entity.

The interpretation of the graph can also include perturbations of entities: one entity is set at a given value for a certain subset of iterations. This allows us to test the model reactions to variations of some entities that may be impacted by other parts of the model.

A set of bioreactions is then deduced from the graph, by replacing each operator node by a bioreaction, where the direct successors are the products of the reaction, and the direct predecessors are reactives or catalysers of the bioreaction, according to whether they are consumed or not. The rates of each reaction depend on the nature of the reaction, the amount of products, and it cannot be directly deduced from the LG, as it is more complex.

The bioreactions are then transformed into a system of ODEs, that is implemented through Novadiscovery's proprietary simulation framework (SimWork). Various tools are used to calibrate the model where values of parameters are unavailable in literature, and to simulate the model over a virtual population and several treatment arms.

RESULTS

- The LG of bile acid metabolism contains synthesis from cholesterol, entero-hepatic transport and regulation of the synthesis, as well a some other entities associated with infection and the diurnal clock.
- The logical model is the interpretation of the LG by the logML software. Initially, the model is interpreted without any perturbations, in order to adapt the reactivity (p) and weakening (q) of the edges to obtain correct behavior. The values are of course not quantitative, but the ratios between entities like conjugated / unconjugated bile acids have to be respected.

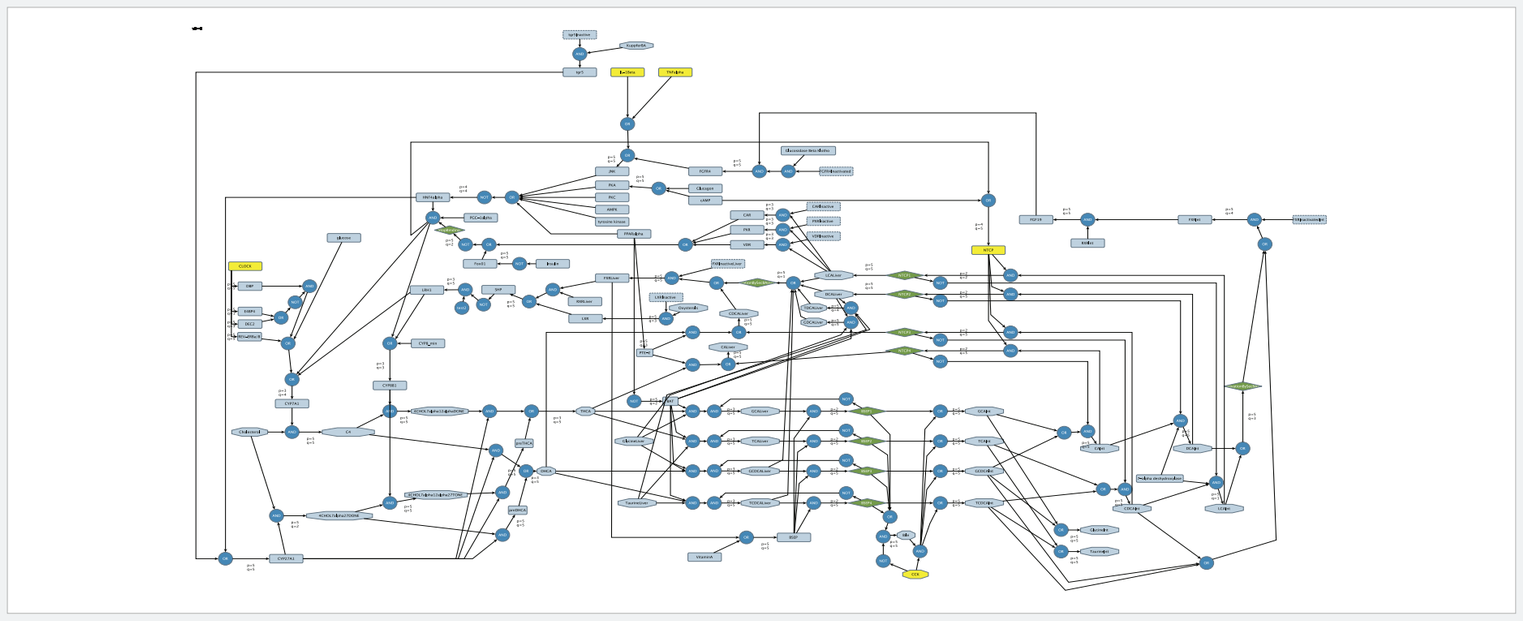

Figure 2: The complete logical graph of the bile acid metabolism. In dark blue are the operator nodes, in green the transporters, in yellow the entities that will be used to test a scenario with a perturbation, and in light blue all the other biological entities.

- We introduce a perturbation on the gene CLOCK entity, that represents the human circadian rhythm. In literature, we found that the synthesis of bile acids follows a daily pattern linked to the CLOCK gene expression

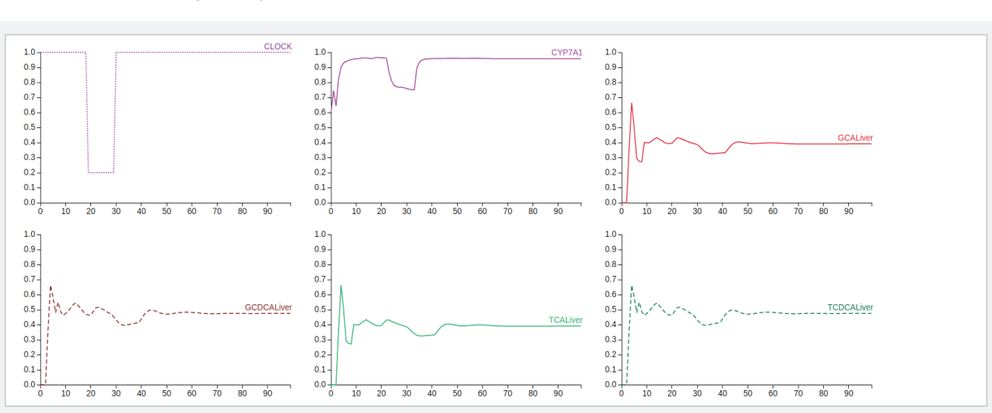

Figure 3: Outputs of the logical model following a perturbation on the CLOCK node. We notice first that the main catalyser of bile acid synthesis, CYP7A1 is reduced, which is followed by a reduction of amount of bile acids. Worth noting also is that the feedback loops lead to a small bump in the bile acid levels after the reduction, and from iteration 75 onwards, we are back at the equilibrium with correct ratios of conjugation.

- Other perturbations are used to test the model, like the impact of inflammation or the deactivation of NTCP, one of the bile acid transporters. The logical model was also used to simplify the model and remove some entities that were considered useless because they were unmeasurable in vivo and their presence in a linear cascade did not add any information to the model.
- The computational model is the translation of the graph into bioreactions. For the simplest reactions, we used mass action laws:

$$a\ .\ A \rightleftarrows b\ .\ B \text{ where } r = k+ * [A]a - k- * [B]b$$

- For reactions that are catalysed by an enzyme or that observe a saturation phenomenon (represented in the LM by q<5), we use Michaelis Mentens:

$$S + E \rightarrow E + P \text{ where } r = Vmax * [S] / (KM+[S]) = kcat * [E] * [S] / (KM+[S])$$

- For more complex reactions, we can use mathematical functions that fit specific data (for example gallbladder emptying), or more classical bioreactions found in literature, like competition for a transporter.

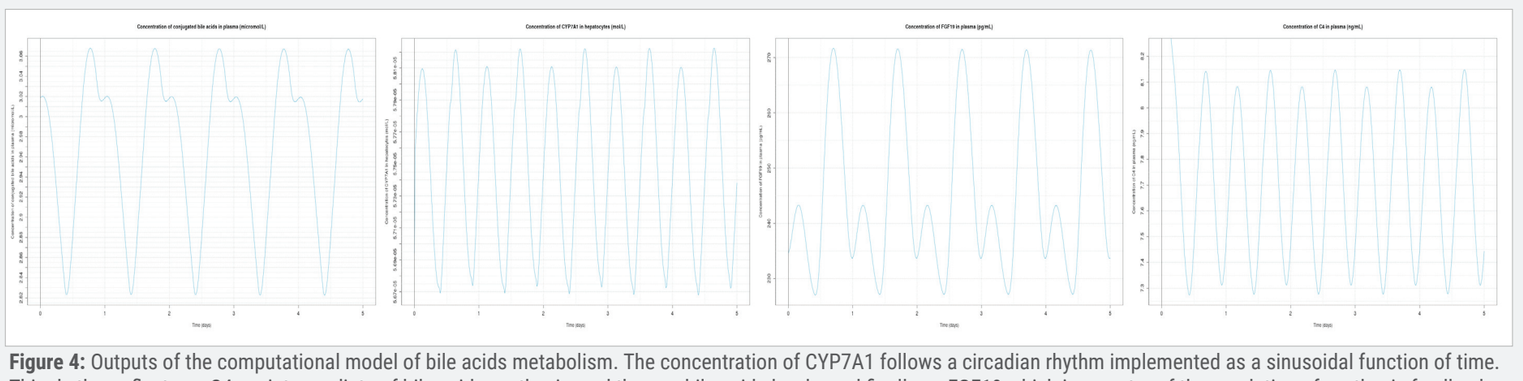

Figure 4: Outputs of the computational model of bile acids metabolism. The concentration of CYP7A1 follows a circadian rhythm implemented as a sinusoidal function of time. This rhythm reflects on C4, an intermediate of bile acids synthesis, and then on bile acids levels, and finally on FGF19 which is an actor of the regulation of synthesis feedback loop.

ACKNOWLEDGEMENTS

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REFERENCES

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DISCUSSION & CONCLUSIONS

- The logical model allows us to explore the models dynamics and check that there is no major missing link in our model that would lead to incorrect behaviour after a given perturbation.
- In this case, it allowed us:
  - To check the exhaustivity of our knowledge or explore and validate hypothesis, particularly concerning regulation of synthesis.
  - To simplify the model before implementing the computational model by reducing the number of entities.
  - To explore the possible impacts of HBV on the bile acids metabolism via transporters blockade and inflammation.
- The computational model was then built using this information, which saved time and complexity.
- In this project for ENYO Pharma, bile acids submodel is central as it contains the target of their treatment, FXR. FXR is an important actor of bile acids regulation, and also a component for HBV replication.

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NOVADISCOVERY, 1 Place Giovanni da Verrazzano, 69009 Lyon, France, contact@novadiscovery.com
ENYO PHARMA, 321 avenue Jean Jaurès, 69007 Lyon, France, contact@enyopharma.com

www.novadiscovery.com