Investigation of the liver's adaptation to acute injury using multi-scale mathematical modeling

Géraldine Celliere

MAMBA team

- Modeling and Analysis for Medical and Biological Applications
- Led by Marie Doumic-Jauffret
- Joint with UPMC
- At Inria, focuses on:
  - mathematical modeling of biological tissues (liver, tumors)
    => Mainly Dirk Drasdo
  - Protein aggregation in amyloid diseases
    => Mainly Marie Doumic-Jauffret

The liver has a number of key functions

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- Production of bile to help digestion
- Carbohydrate, lipid and protein metabolism (storage or release of glucose, cholesterol, vitamins depending on the need)
- Detoxification of toxins (pollutants) and drugs
- Detoxification of ammonia (NH_4^+)

The liver is also subjected to diseases

- Infections such as Hepatitis
- Cancer
- Steatosis (accumulation of fat droplets)
- Cirrhosis (accumulation of scar tissue, mainly due to alcoholism)
- Drug damage (mainly due to paracetamol overdose)

The liver is also subjected to diseases but can regenerate

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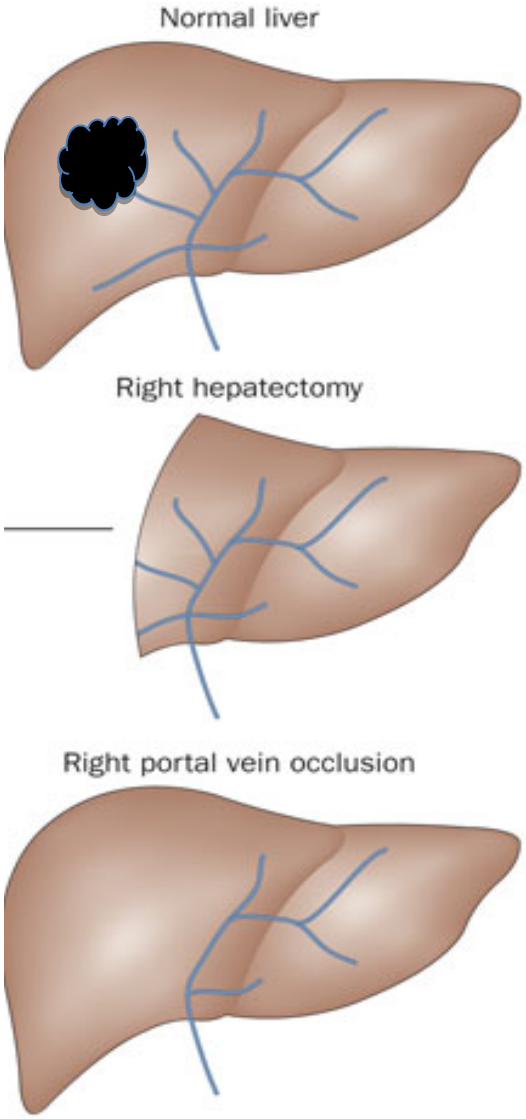
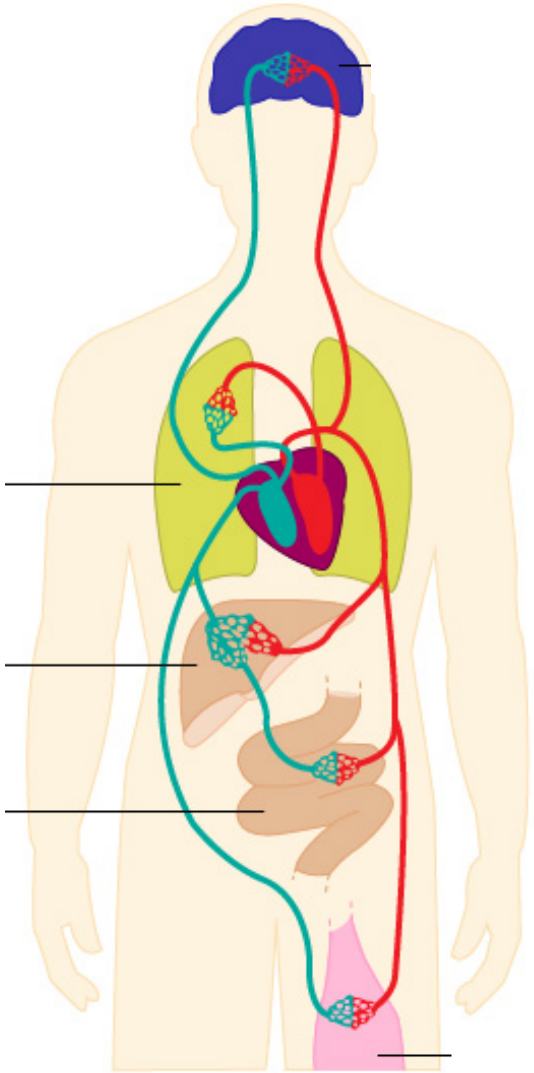


Ammonia is involved in life-threatening complications



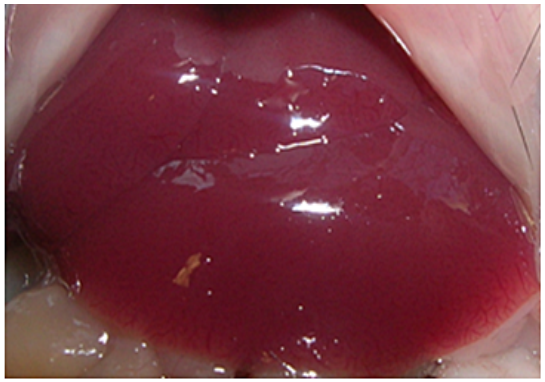
- NH4 enters the blood in the intestine. The blood continues to the liver, where ammonia is metabolized
- In case of NH4 detoxification impairment, hepatic encephalopathy can occur
- Current treatments of hyperammonemia perform poorly
- The main cause of acute liver failure is paracetamol (acetaminophen) overdose

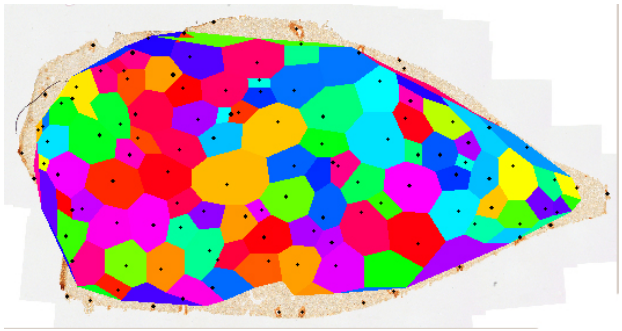
Question

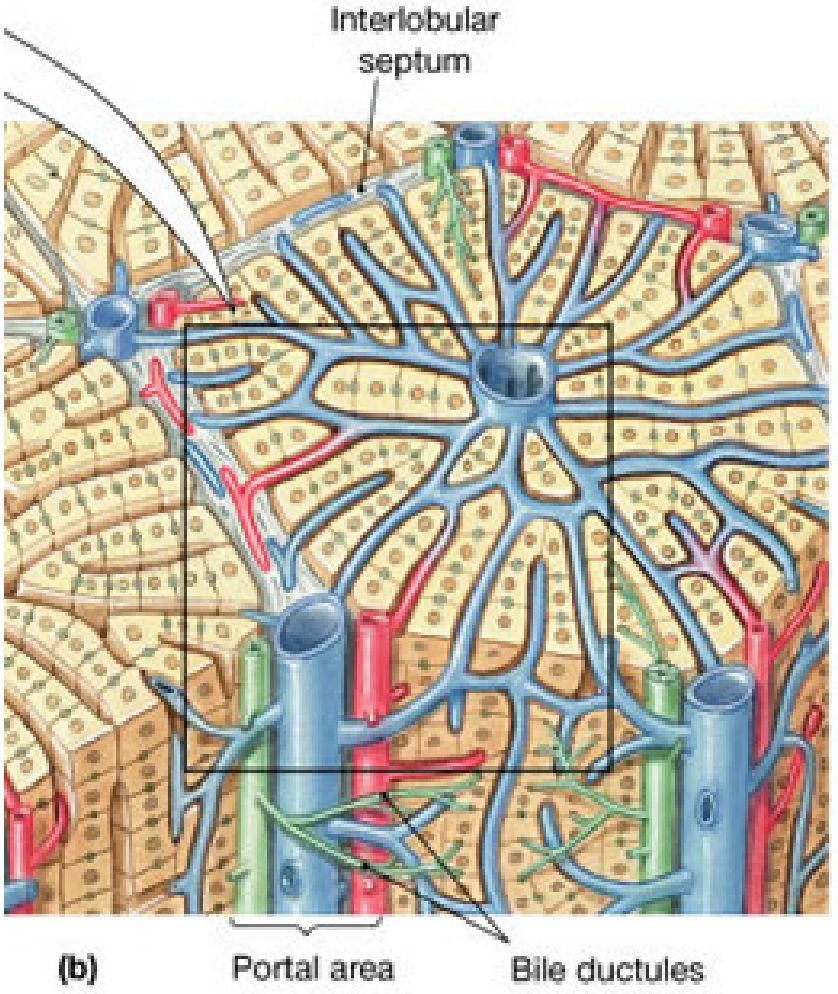
How is ammonia metabolism modified in the liver in case of acute damage ?

Integrated metabolic spatial-temporal model for the prediction of ammonia detoxification during liver damage and regeneration, *Hepathology (2014)* Schliess S., Hoehme S., Henkel S. G., Ghallab A., Driesch D., Böttger J., Guthke R., Pfaff M., Hengstler J. G., Gebhart R., Häussinger D., Drasdo D., Zellmer S.

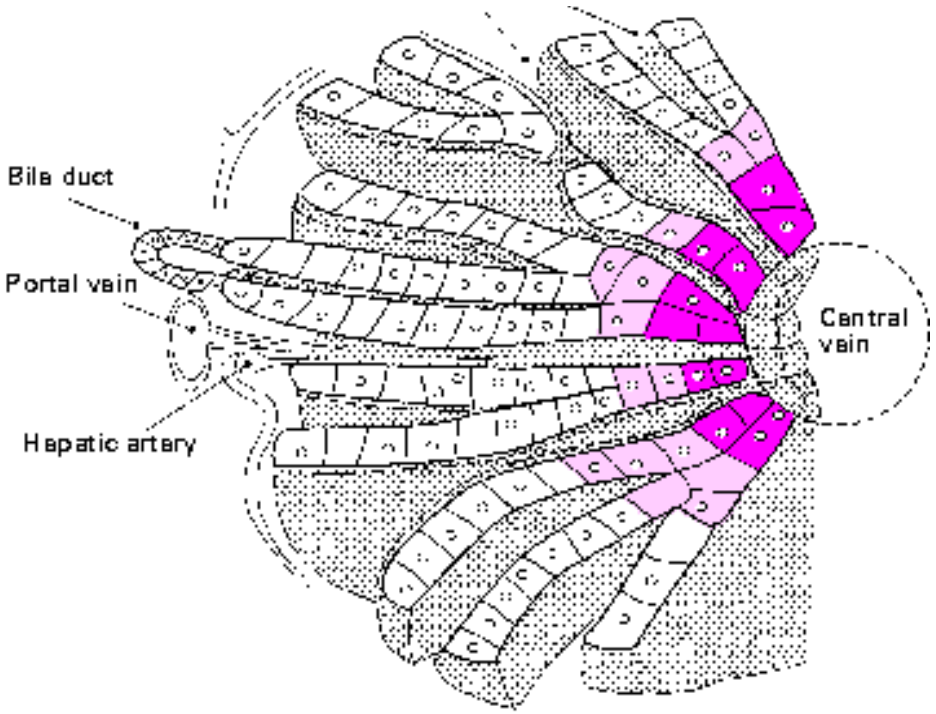
The liver has a complex architecture







Zonation of metabolic functions



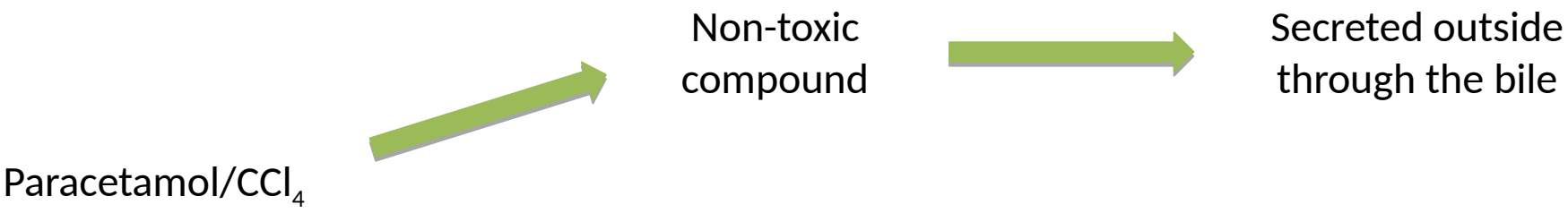
Ammonia detoxified through the urea cycle
- High capacity, low affinity

Ammonia detoxified through glutamine synthetase
- Low capacity, high affinity

No drug detoxification

Drug detoxification

Mechanisms of paracetamol toxicity



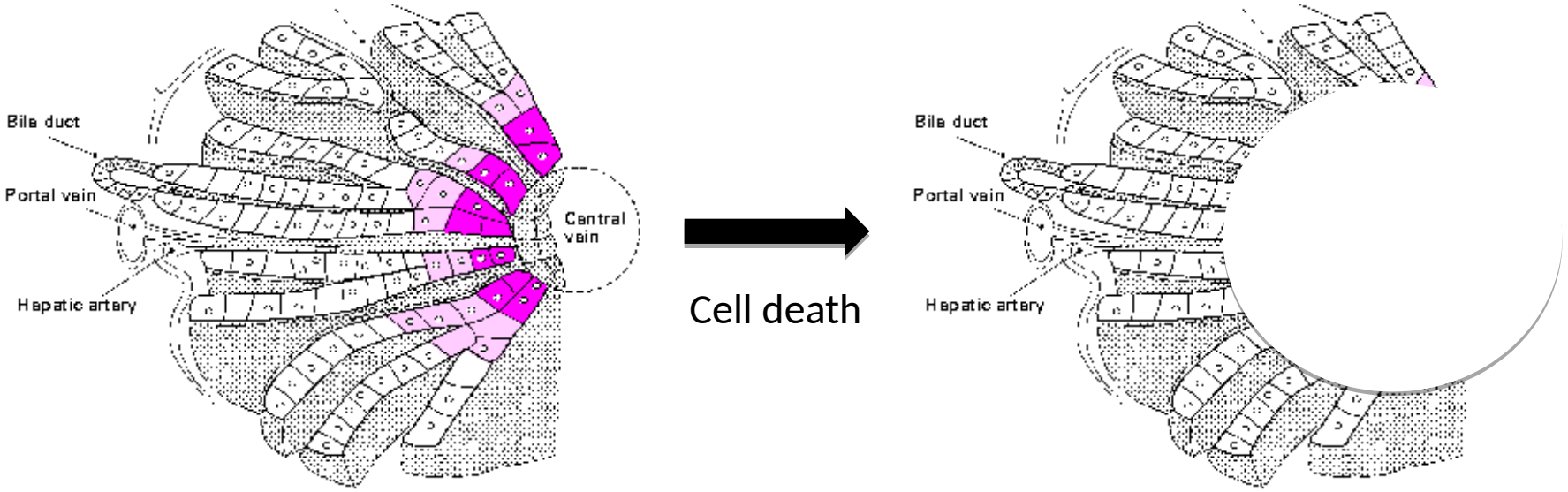
Mechanisms of paracetamol toxicity

Paracetamol/CCl_4

Saturation

Non-toxic compound → Secreted outside through the bile

Toxic compound → Cell death



What is mathematical modeling?

Blood influx

[metabolites]

Liver

V(t)

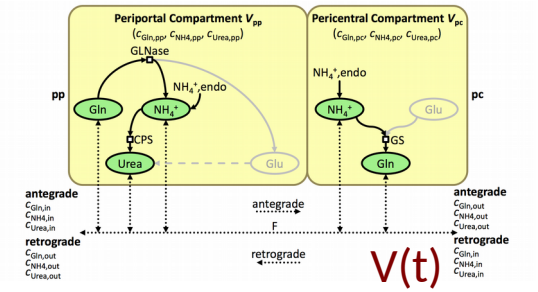
Blood efflux

[metabolites]

compare

Blood influx

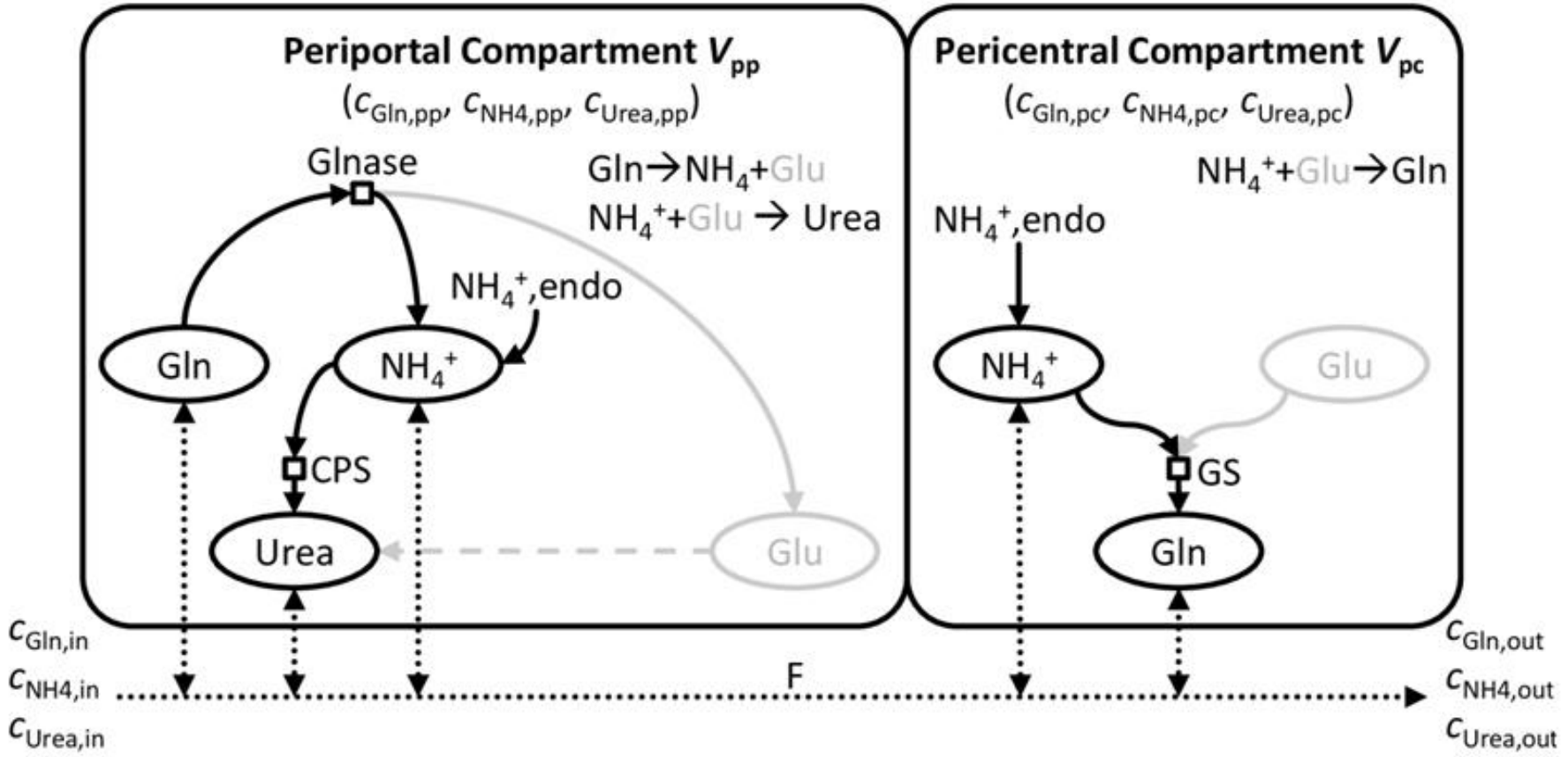
[metabolites]



Blood efflux

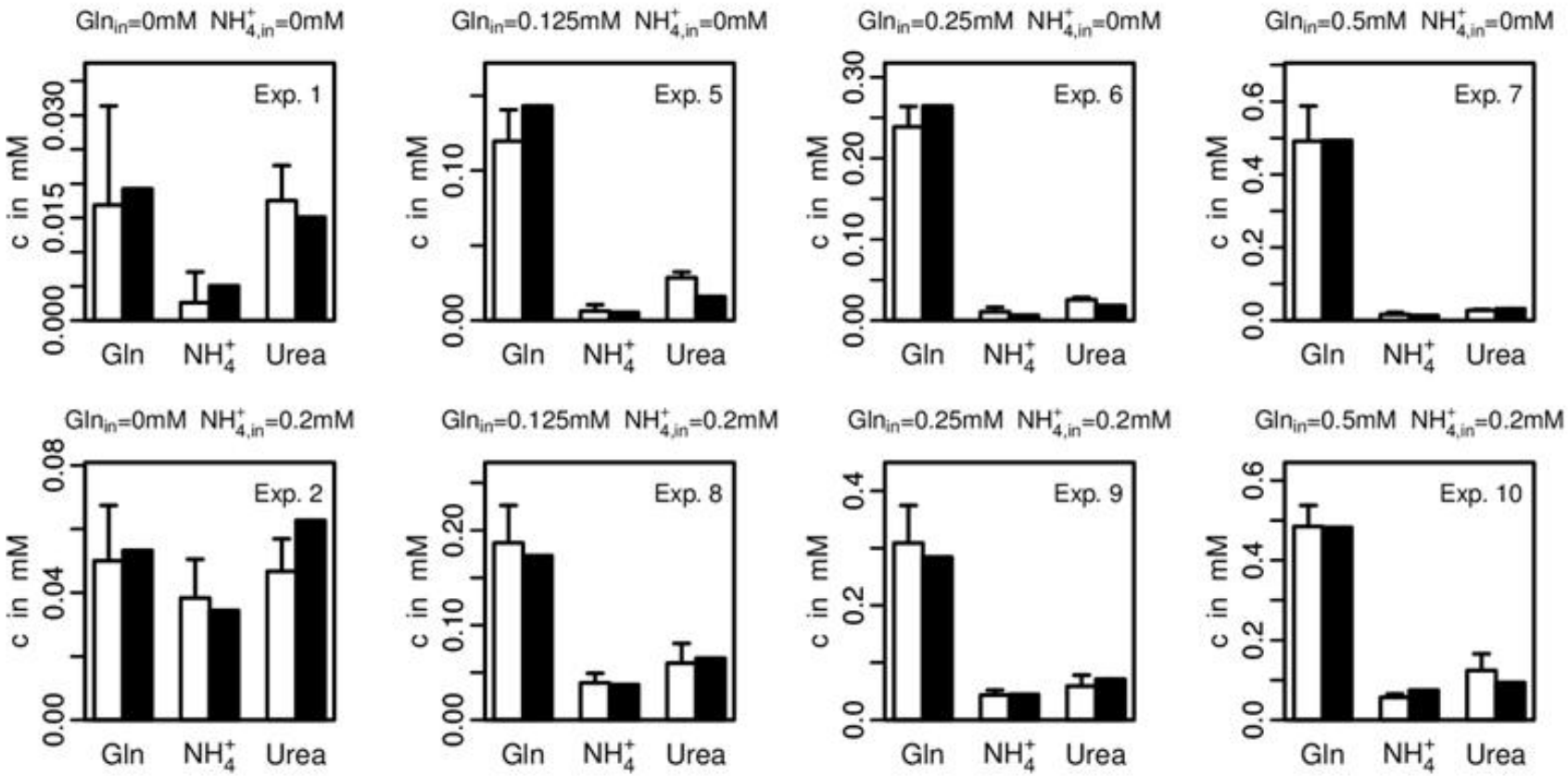
[metabolites]

Step 1: build a model of NH4 detoxification



$$V_{pp}\frac{\partial c_{NH4,pp}}{\partial t} = (v_{GS} - v_{CPS})V_{pp} + (c_{NH4,in} - c_{NH4,pp})F$$

Step 2: Calibration of the metabolic model with data of healthy livers



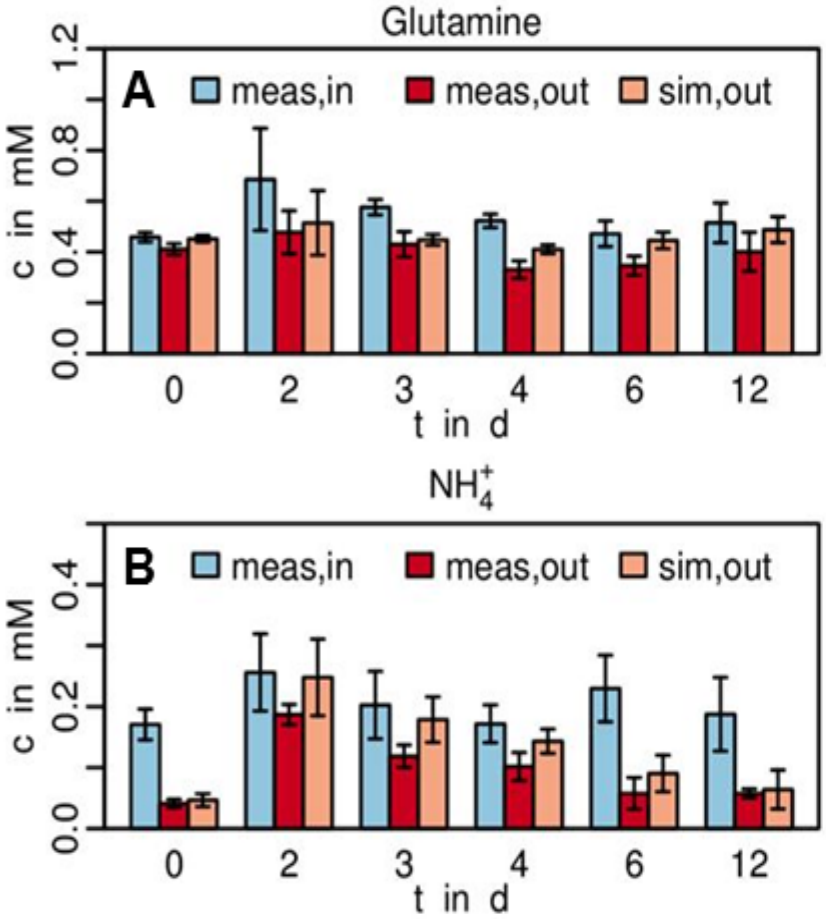
Good agreement

Step 3: Simulate the classical scheme in case of liver damage

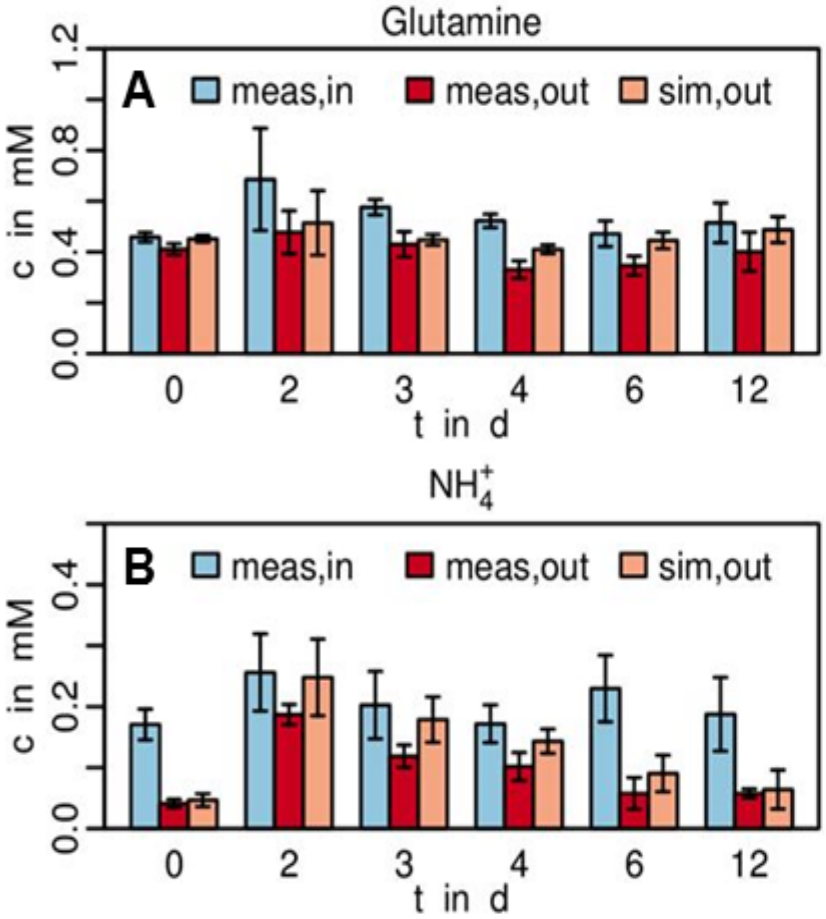
Will we be able to reproduce the measured metabolites concentrations in the case of a damage if we assume that the reaction are the same but part of the liver is destroyed (changed volumes) ?

$$V_{pp}(t)\frac{\partial c_{NH4,pp}}{\partial t} = (v_{GS} - v_{CPS})V_{pp}(t) + (c_{NH4,in} - c_{NH4,pp})F$$

Step 3: Simulate the classical scheme in case of liver damage

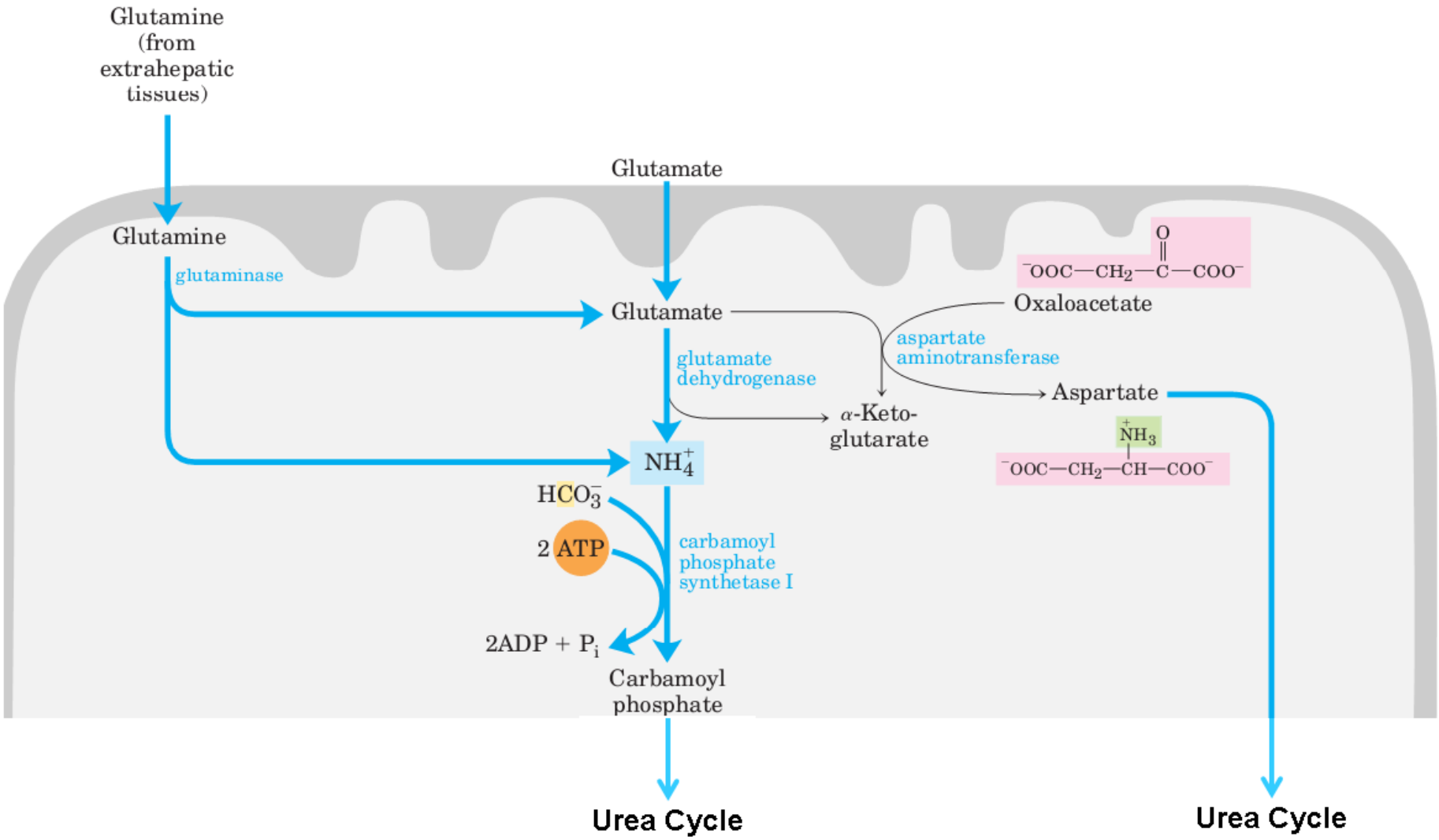


Step 3: Simulate the classical scheme in case of liver damage



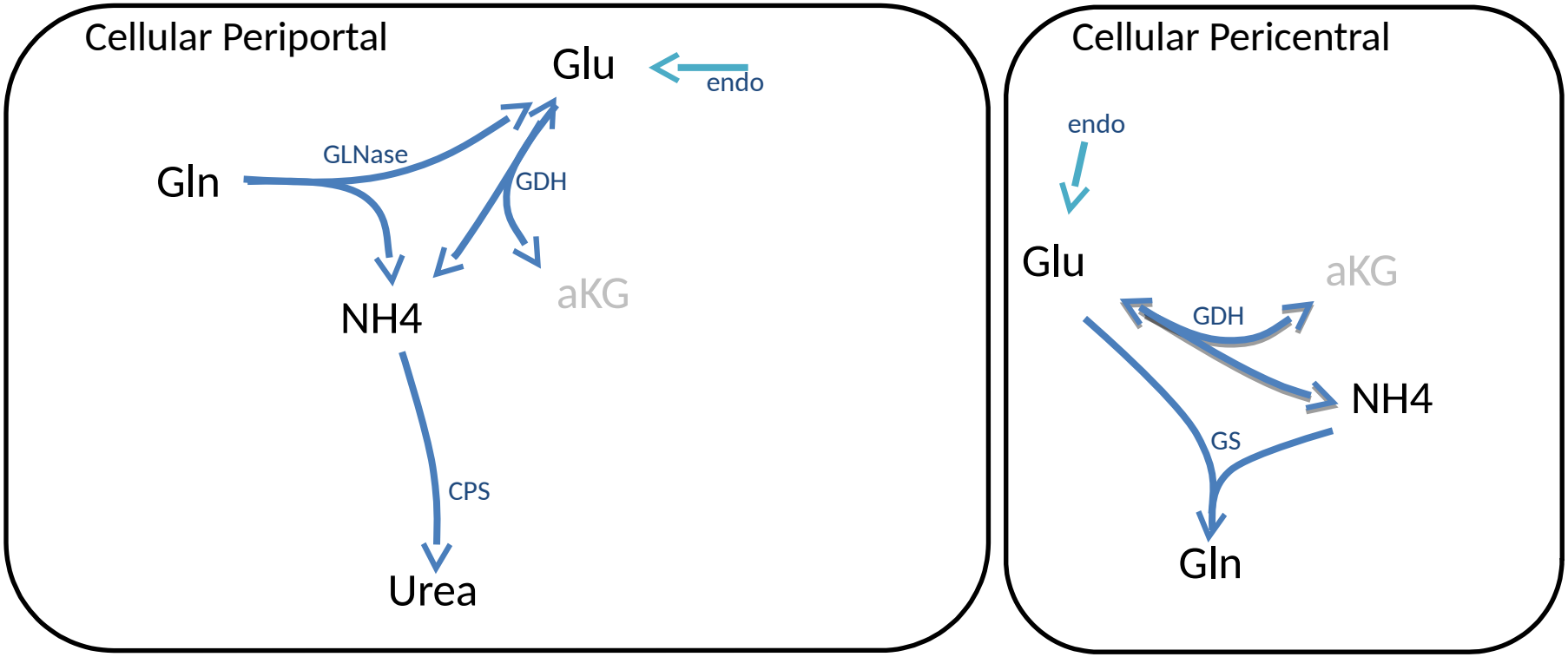
There is something missing in the model …

Step 4: Asking the experimentalists



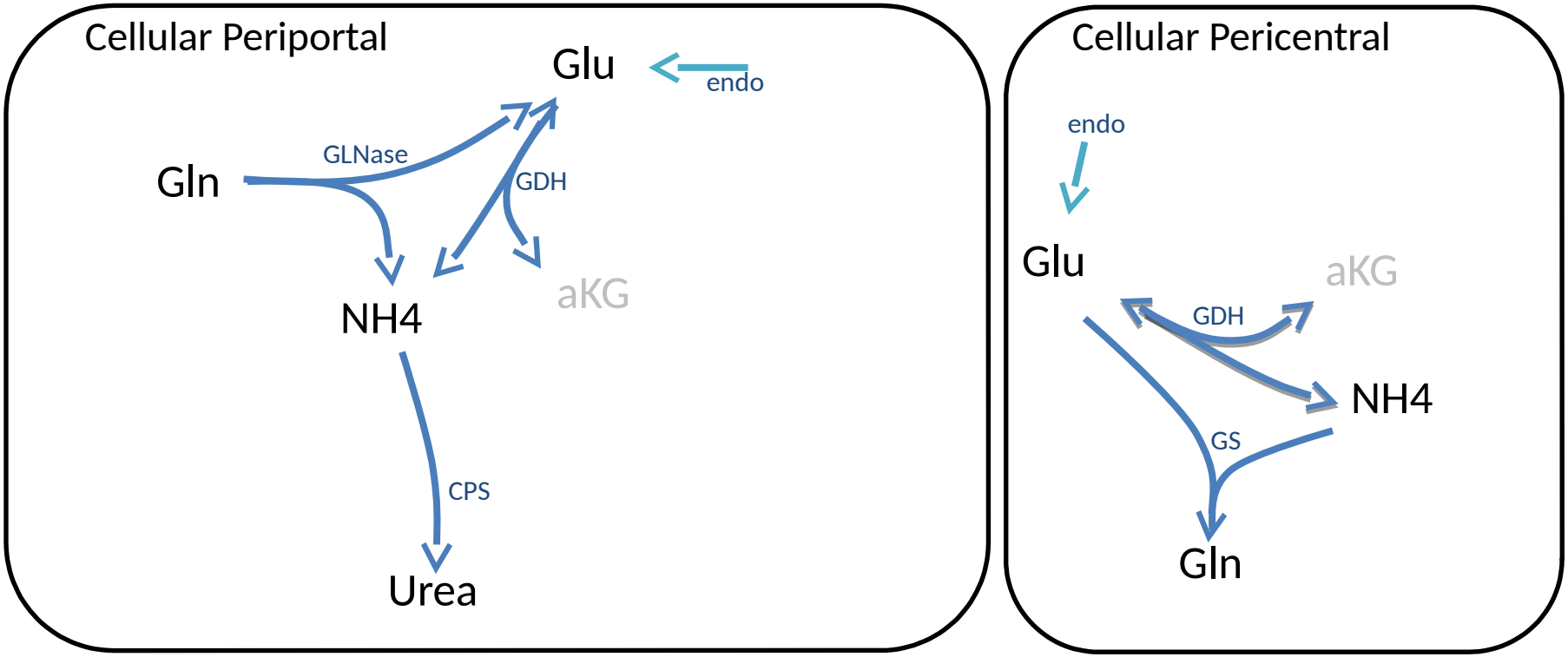
Step 4: Asking the experimentalists

Step 5: Adding the GDH reaction to the model



- Will the new model be able to reproduce both the data from the healthy case and from the drug-induced damage case ?
- What will be the direction of GDH over time in the damaged case ?

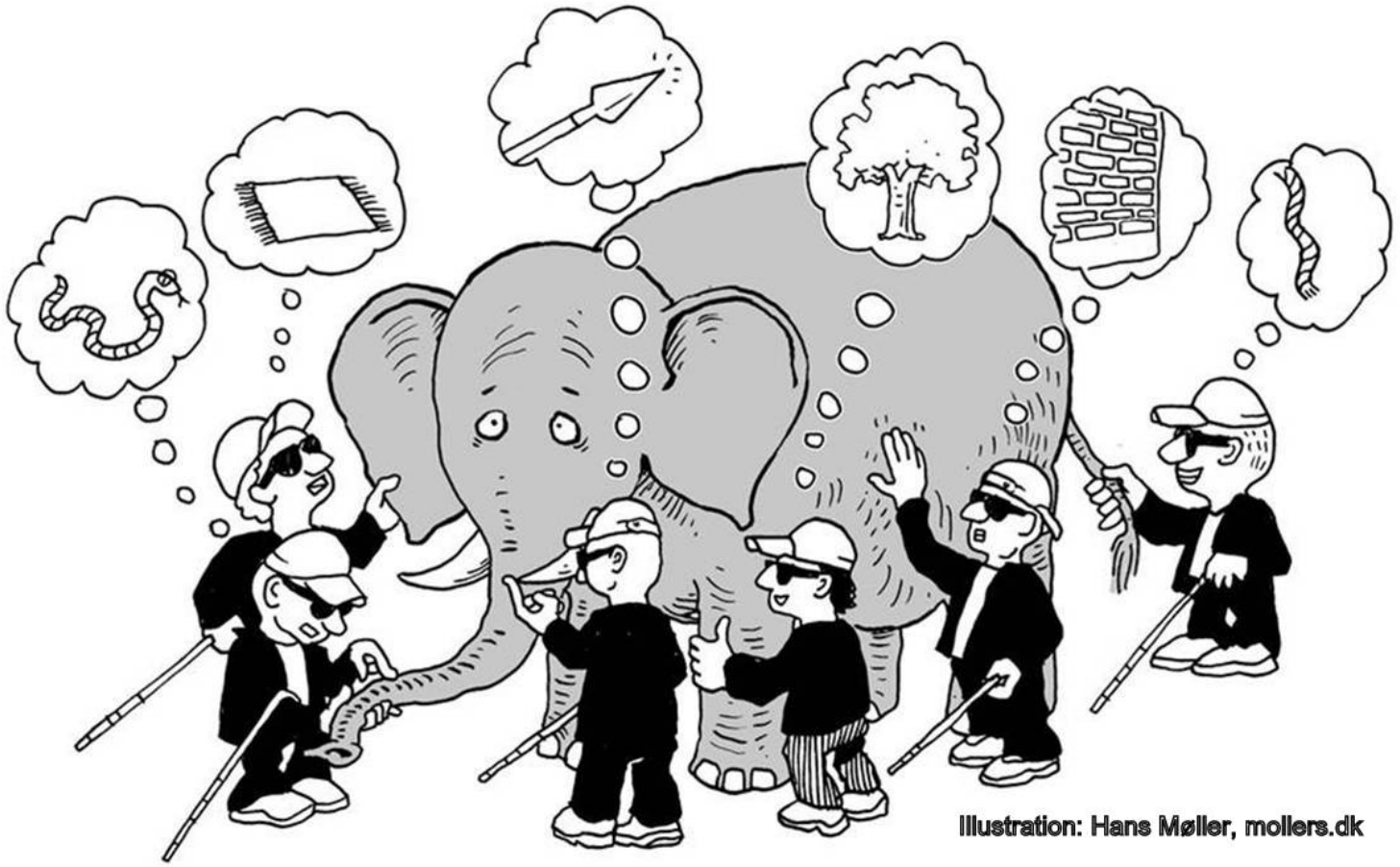
Step 5: Adding the GDH reaction to the model – Open questions



- How to deal with “boundary conditions” ?
- When is a match between model and data good enough ?

Why is modeling useful?

1. Putting together a coherent picture of an entire system – organizing the knowledge



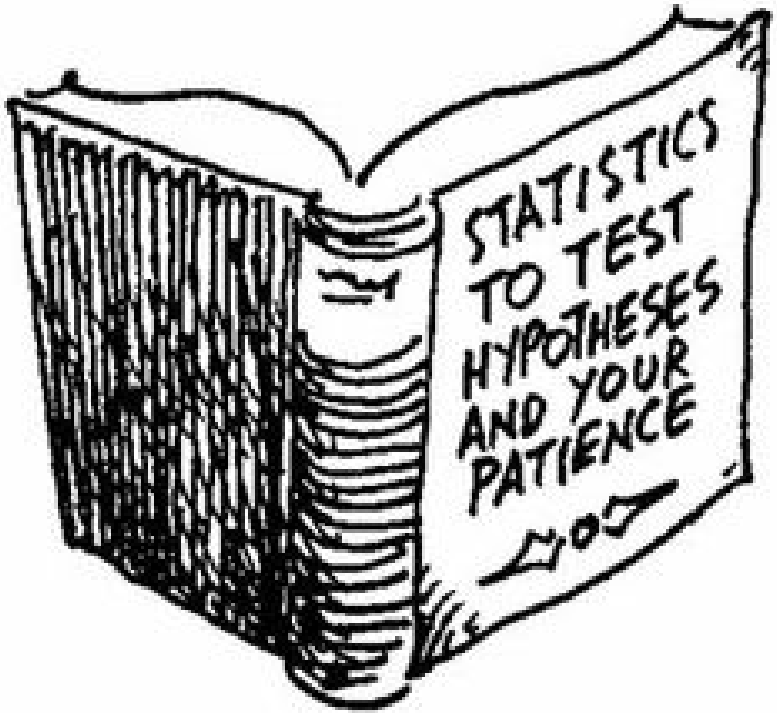
Why is modeling useful?

2. Testing the plausibility of hypotheses

How does the liver regenerate ?

a) Cells proliferate
b) Cells proliferate + migrate towards center
c) Cells proliferate + migrate towards center + cell division is aligned along the blood vessels

With modeling we could show that hypotheses a) and b) are not possible.



Why is modeling useful?

3. Guiding new experiments

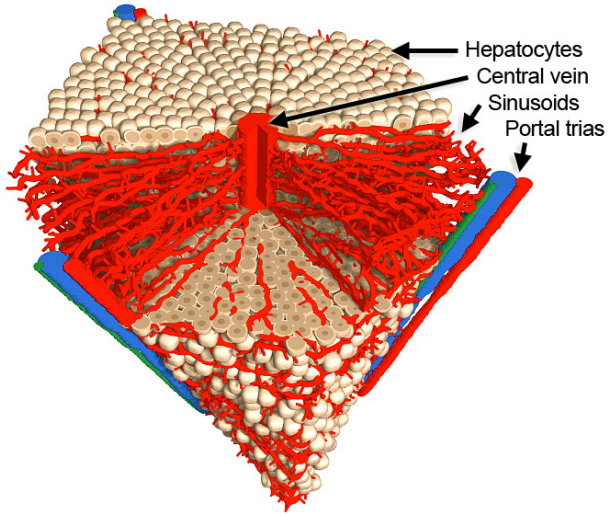
Why is modeling useful?

4. Explore situations that are unreachable or too costly for experiments

Extrapolation from animal to human and from *in vitro* to *in vivo*

Conclusion

- The classical ammonia detoxification scheme cannot explain the observations during liver damage
- GDH might be an important enzyme in this process
- Modeling can really help in biology
- Perspective: investigate the influence of the spatial geometry by replacing the compartment model by a spatially resolved model



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