In silico assessments for placental transfer of small molecules and biologics

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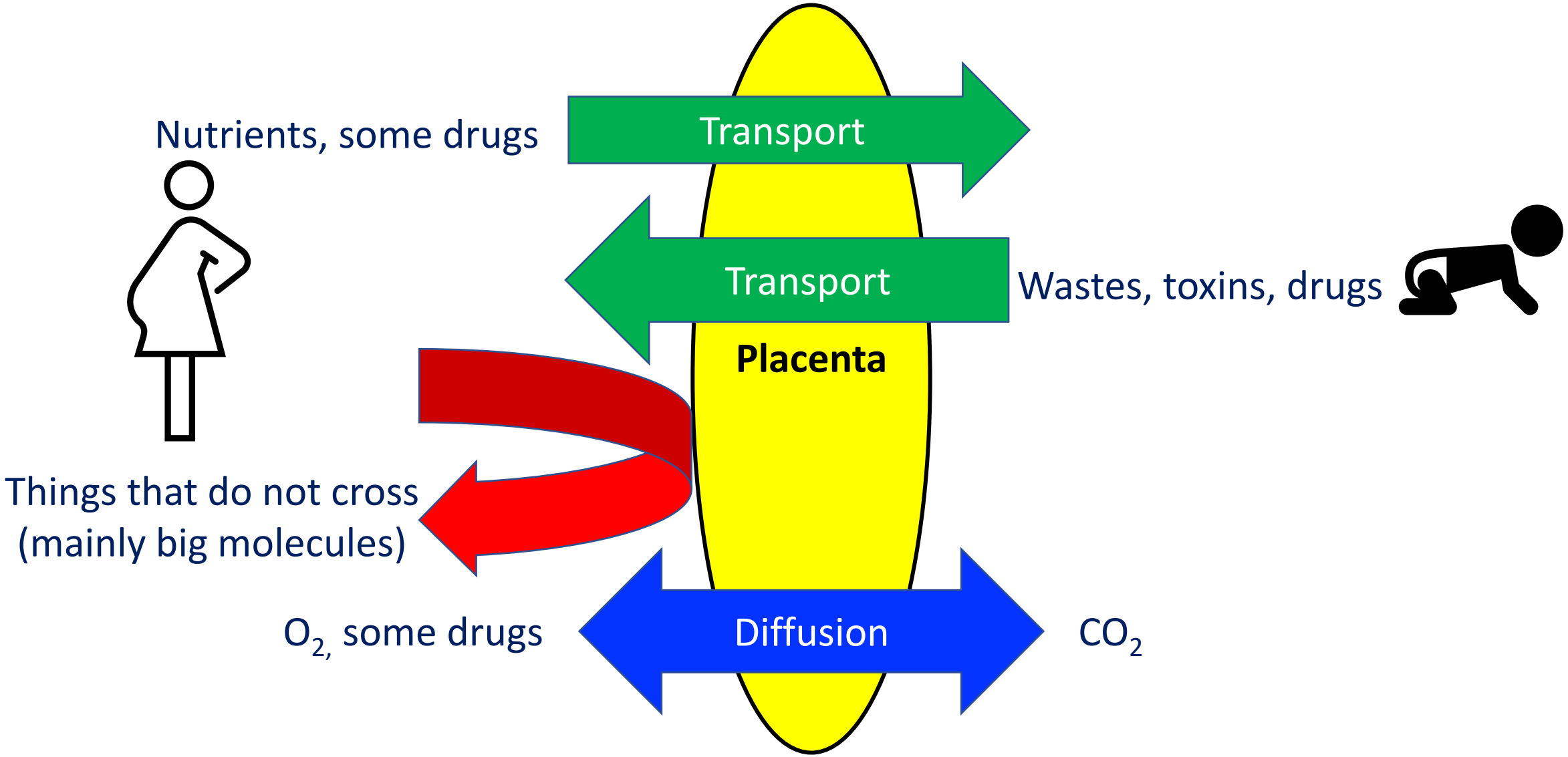
Declarations
Research Funding: BBSRC, Leverhulme Trust, Wellbeing of Women, Rosetrees Trust, Wessex Medical Research
Paid Speaking: Wyeth Nutrition

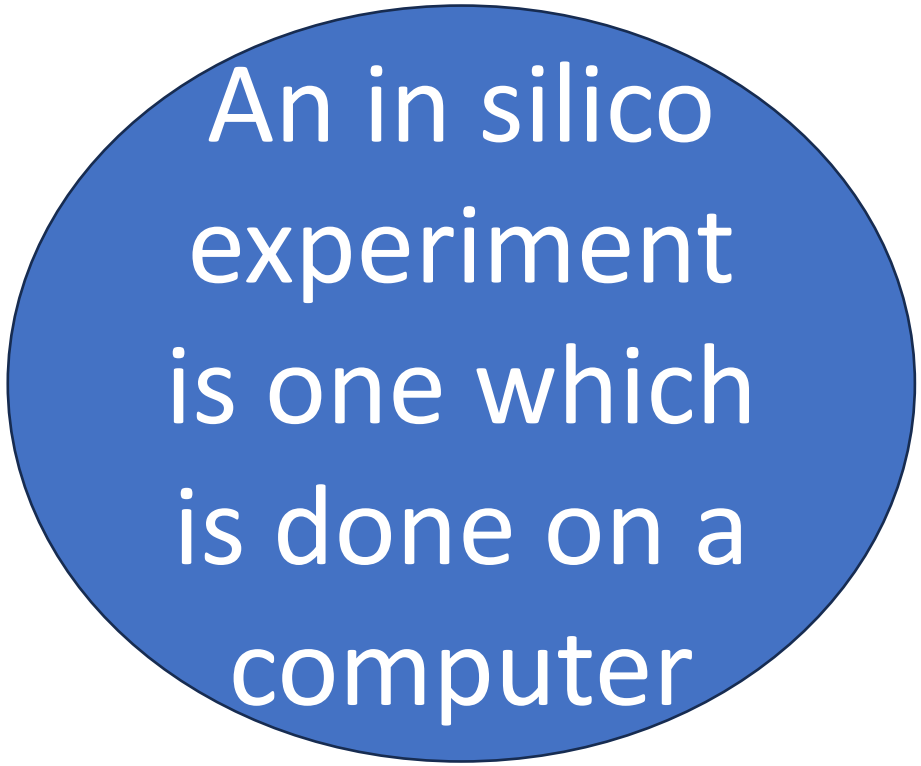
The placenta determines fetal exposures



In silico approaches to study placental transfer

Computational modelling

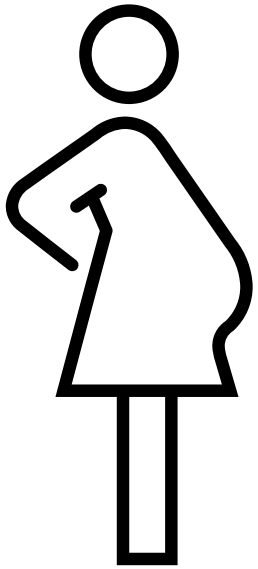
Algorithmic approaches



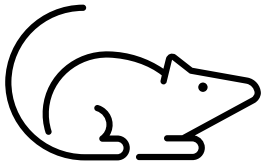
Bioinformatics

Machine learning

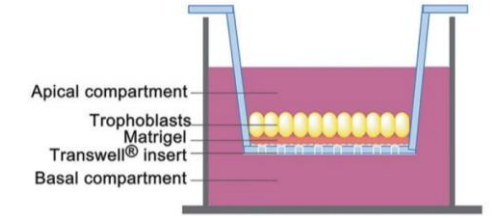
What can you study in silico?

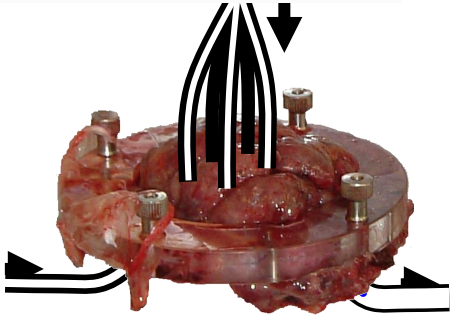


People



Animal models





Placental perfusion

In vitro models

Predicting novel drug protein interactions

Predict genotype drug interactions

Experiments provide data, so why in silico?

- Models can test the biological understanding
- Understanding model systems
- Cheaply and quickly make predictions for multiple conditions
- Explore questions that are difficult to assess experimentally
    - e.g. different stages of gestation
- Models can help design the right experiment

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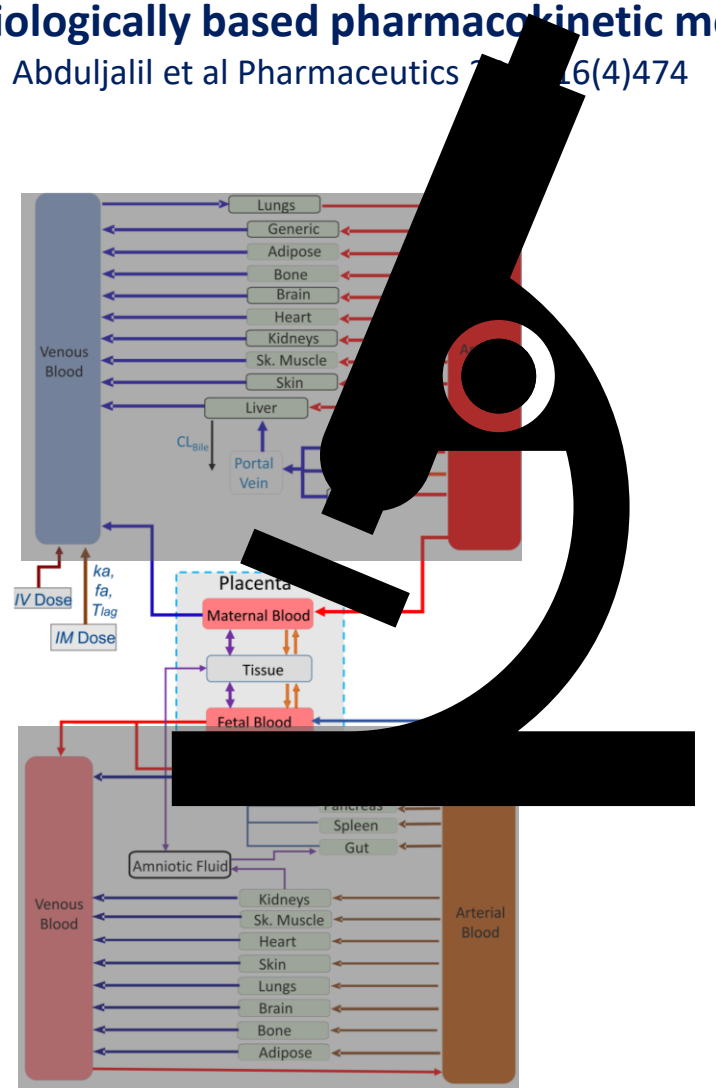
Computational modelling of placental transfer

Modelling placental transfer

Physiologically based pharmacokinetic model

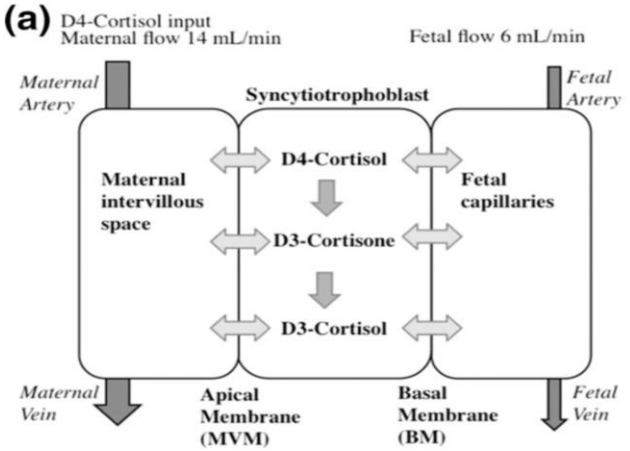
Abduljalil et al Pharmaceutics 7 [illegible] 16(4)474



Iterative model development

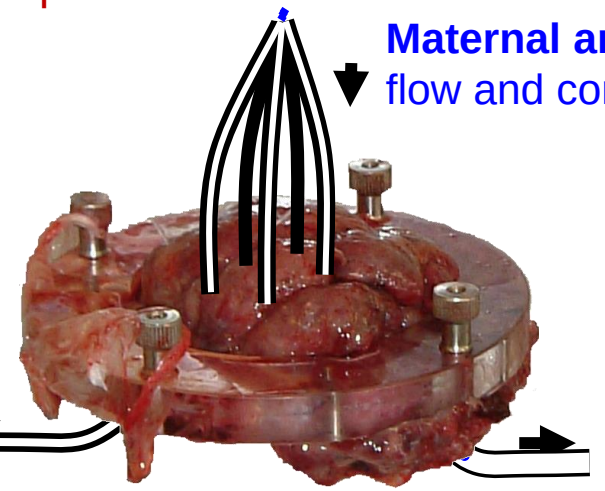
Compartmental model for placental cortisol transfer and metabolism

Stirrat, et al. (2018). J Clin Endocrinol Metab 103(2): 640-648.



Placental perfusion allows well defined conditions

Maternal artery known flow and composition

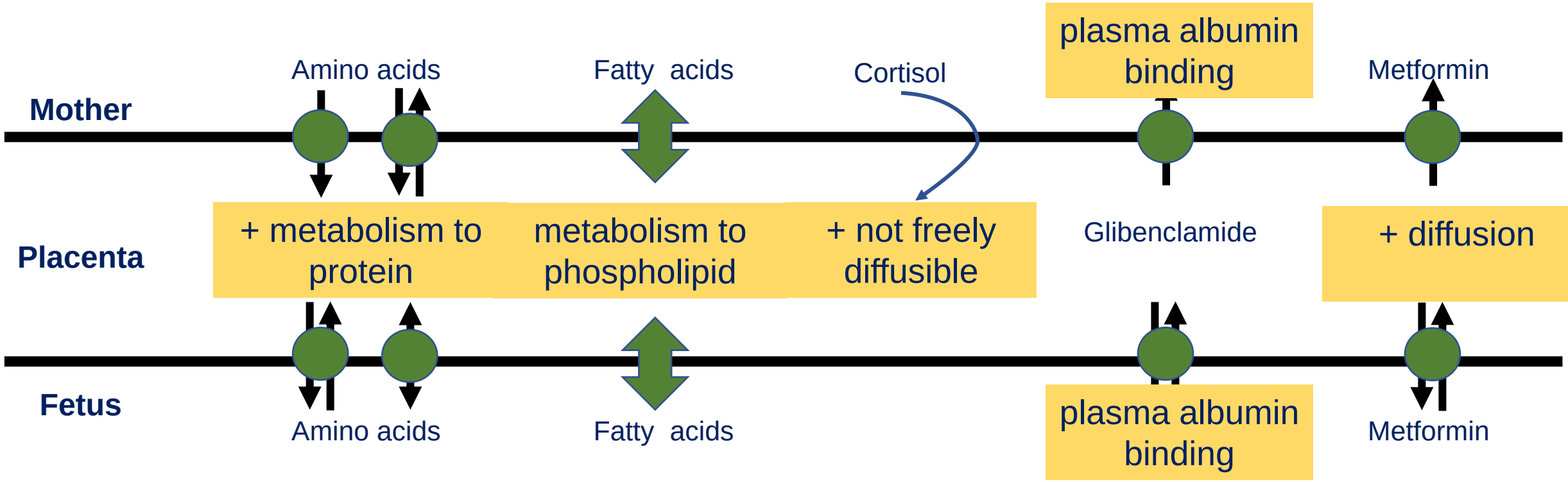


Fetal artery

Fetal vein:

Modelling to make sure we understand the biology

Compound	Amino acids	Fatty acids	Cortisol	Glibenclamide	Metformin
What controls transfer	Metabolism + transporters	Metabolism	Diffusion rate	Plasma binding protein	Diffusion



Lofthouse et al.
Am J Physiol 2015
2016310:R828-36

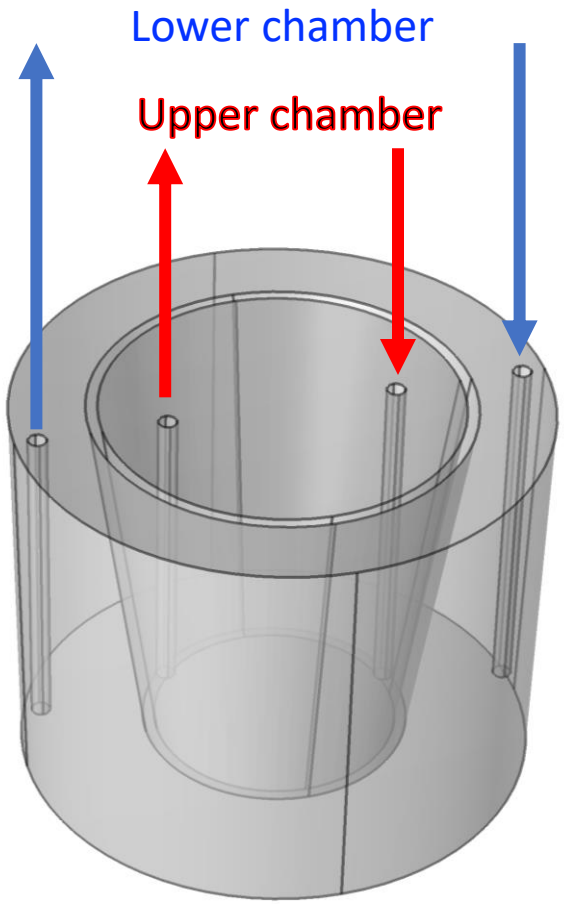
Perazzollo et al.
J Lipid Res 2017
58:443-454

Stirrat et al.
J Clin Endo Metab
2018 103:640-648

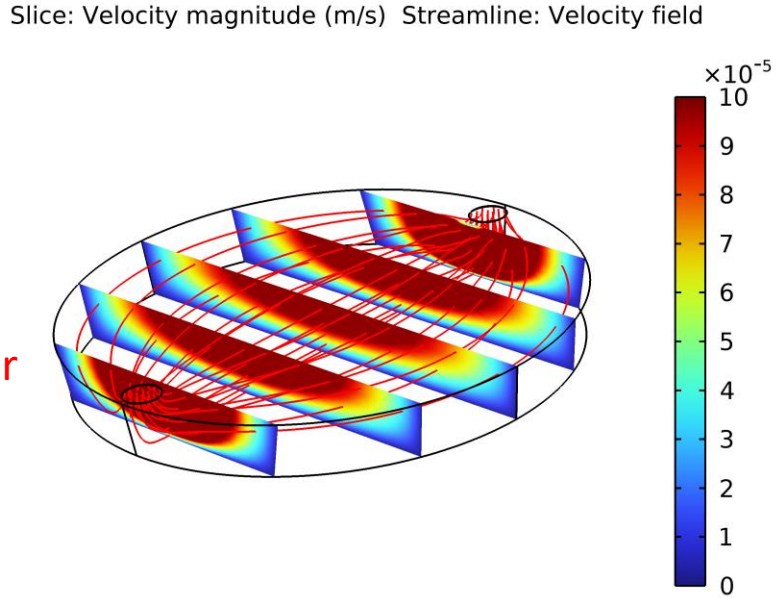
Lofthouse et al.
Eur J Pharm Sci 2020
152:105436

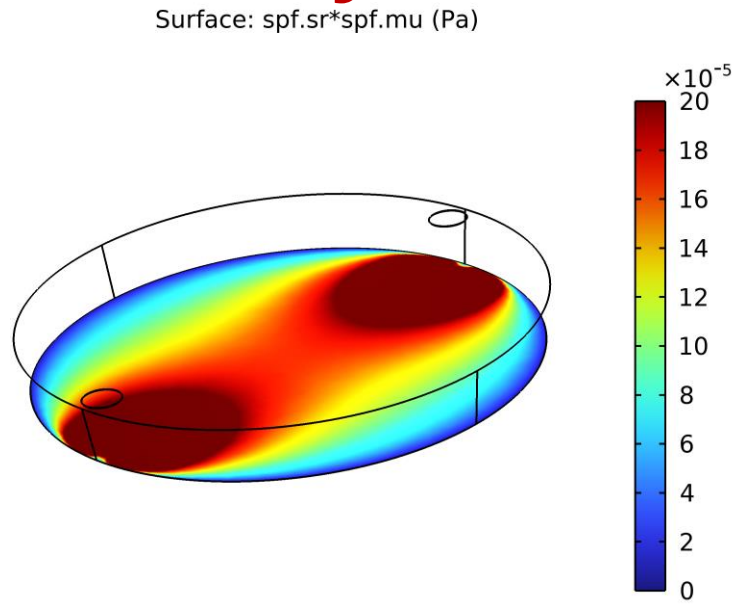
Lofthouse et al.
J Pharm Sci 2023
112:2570-2580

Modelling to better understand model systems

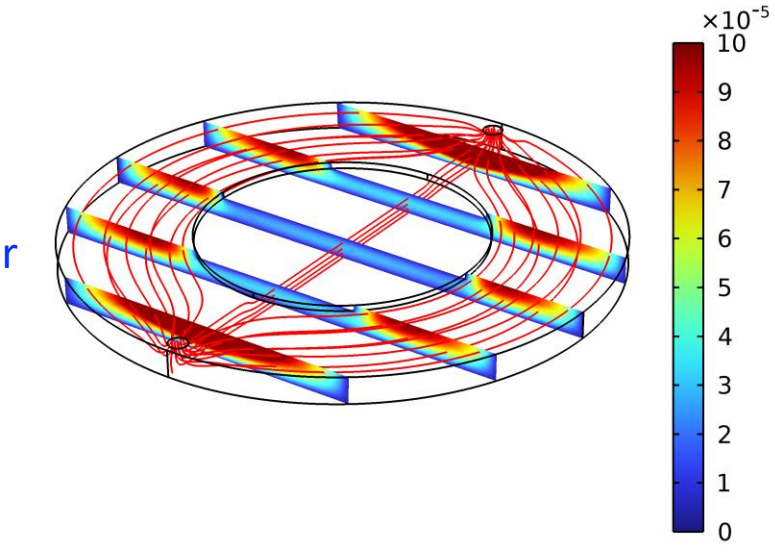


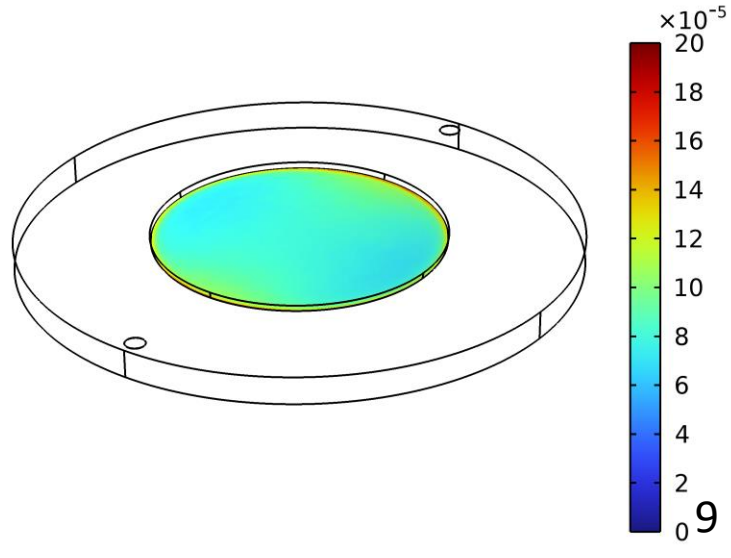
Flow in
Upper chamber





Flow in
Lower chamber

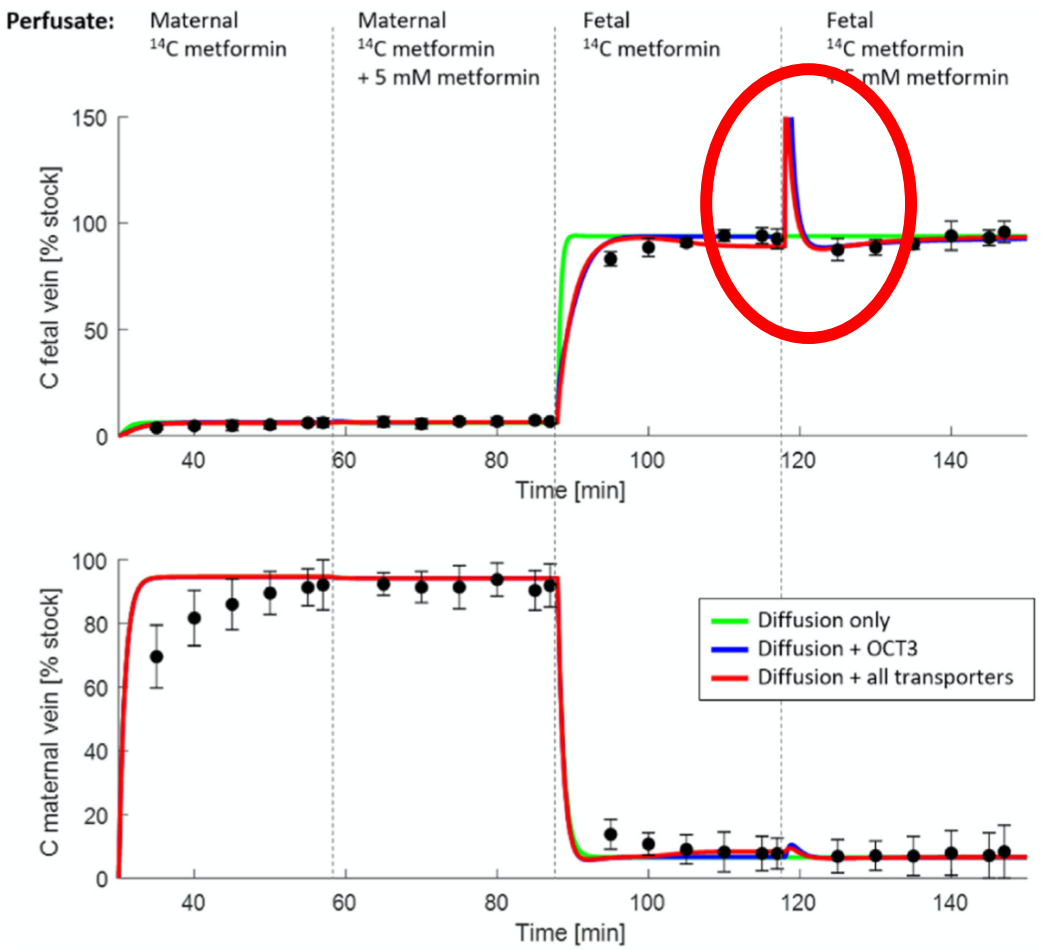




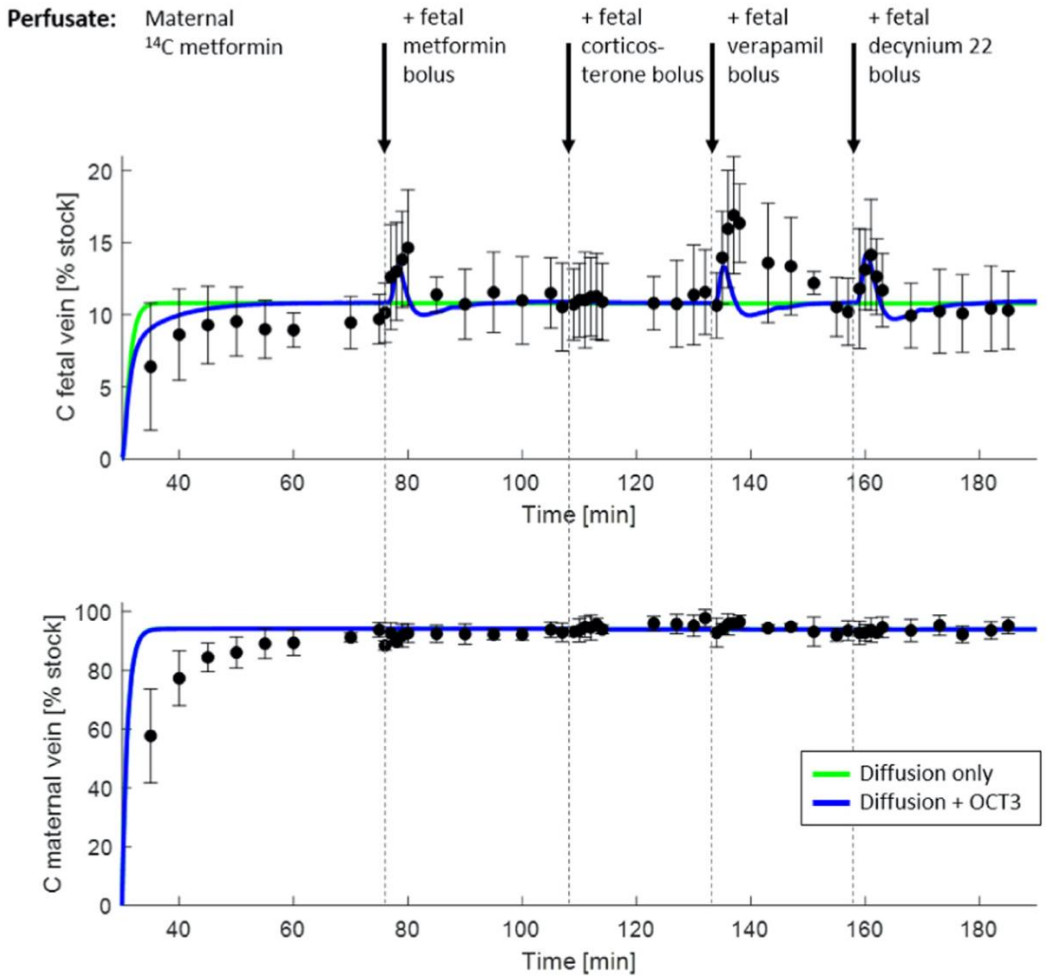
Modelling can design better experiments

Design 1, no data collected at the point where interesting things happen

E.M. Lofthouse et al. / Journal of Pharmaceutical Sciences 112 (2023) 2570–2580



Design2, lots of data points to catch the action!



Modelling placental antibody transfer

A recent paper which covers a similar area is worth a look. Wessel RE, Dolatshahi S (2023) Quantitative mechanistic model reveals key determinants of placental IgG transfer and informs prenatal immunization strategies. PLoS Comput Biol 19(11): e1011109

Immunoglobins and immunotherapy

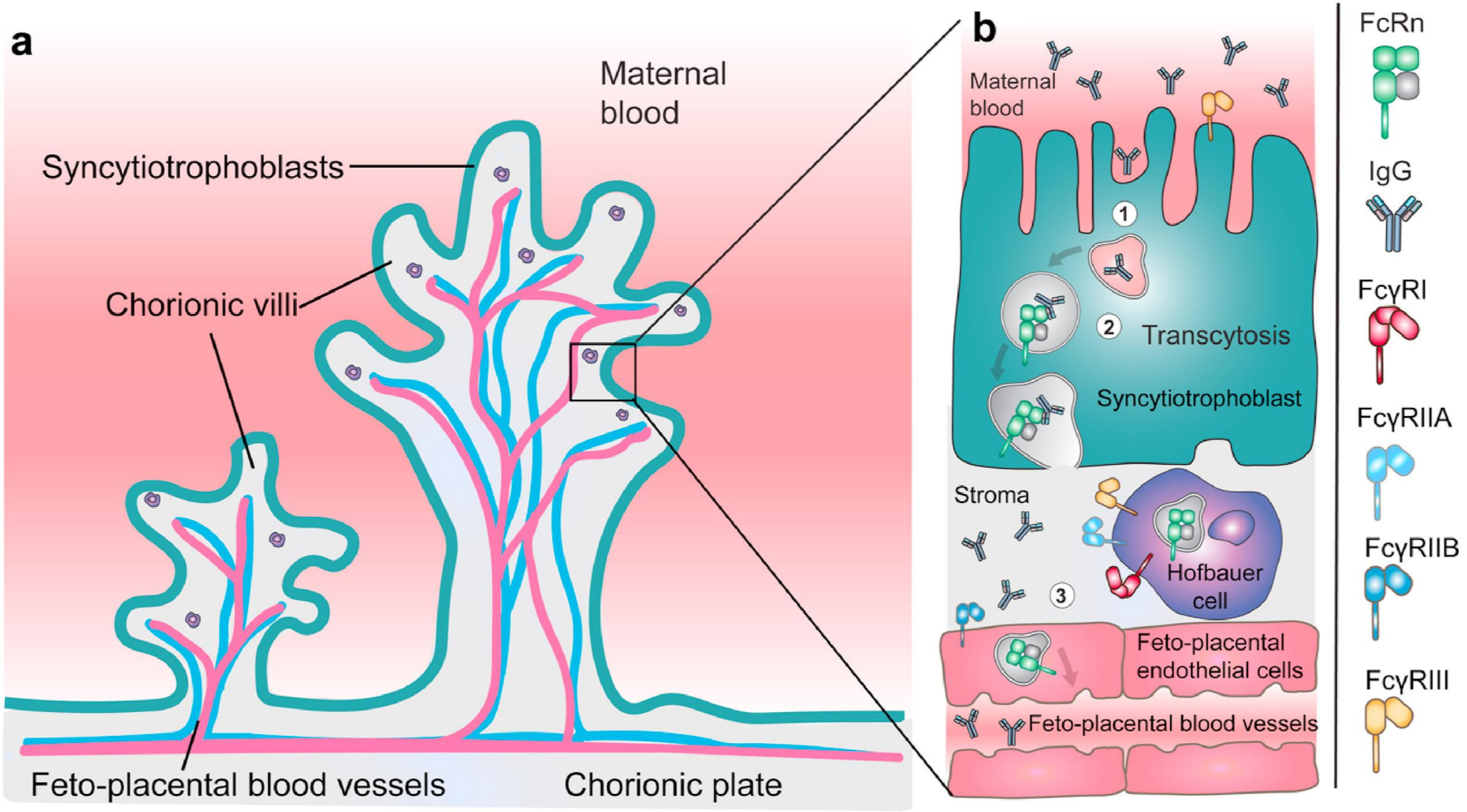
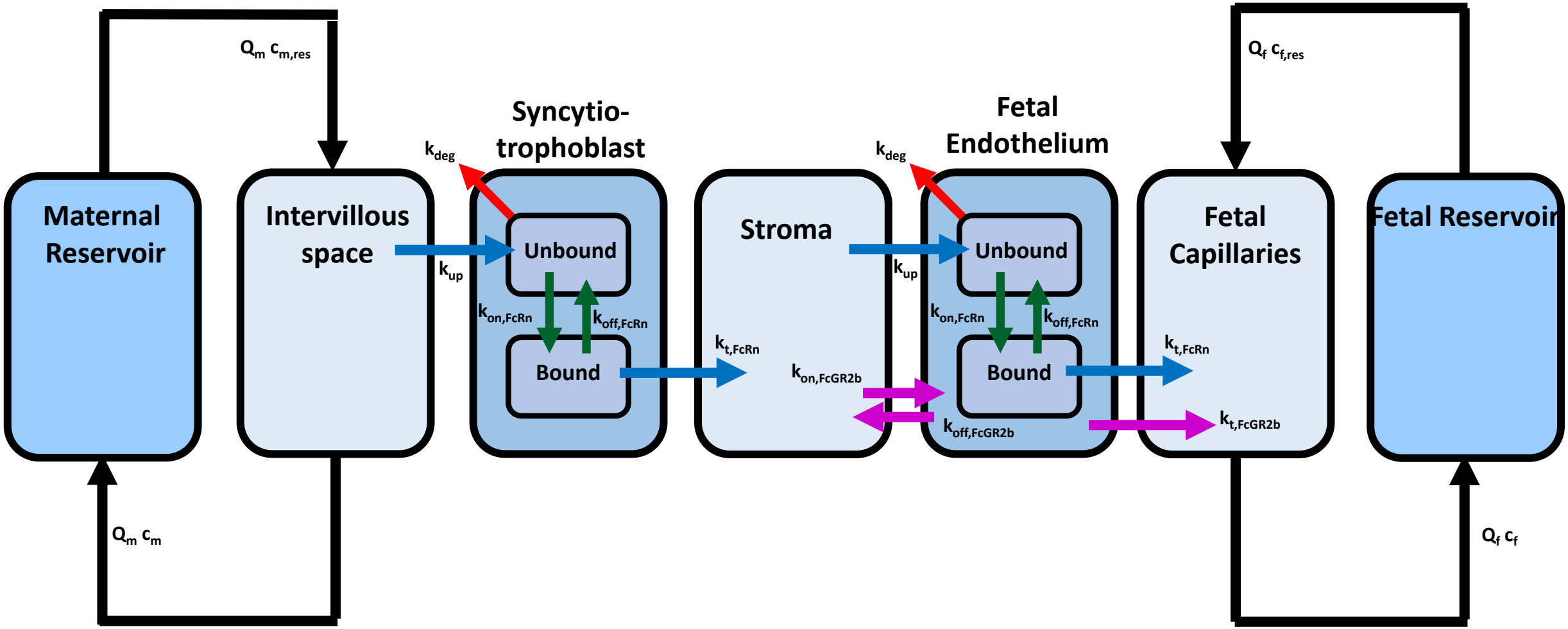


Image Credit: [Sand et al. (2022)]

A model framework for antibody transfer



Single cell RNAseq data can inform the models

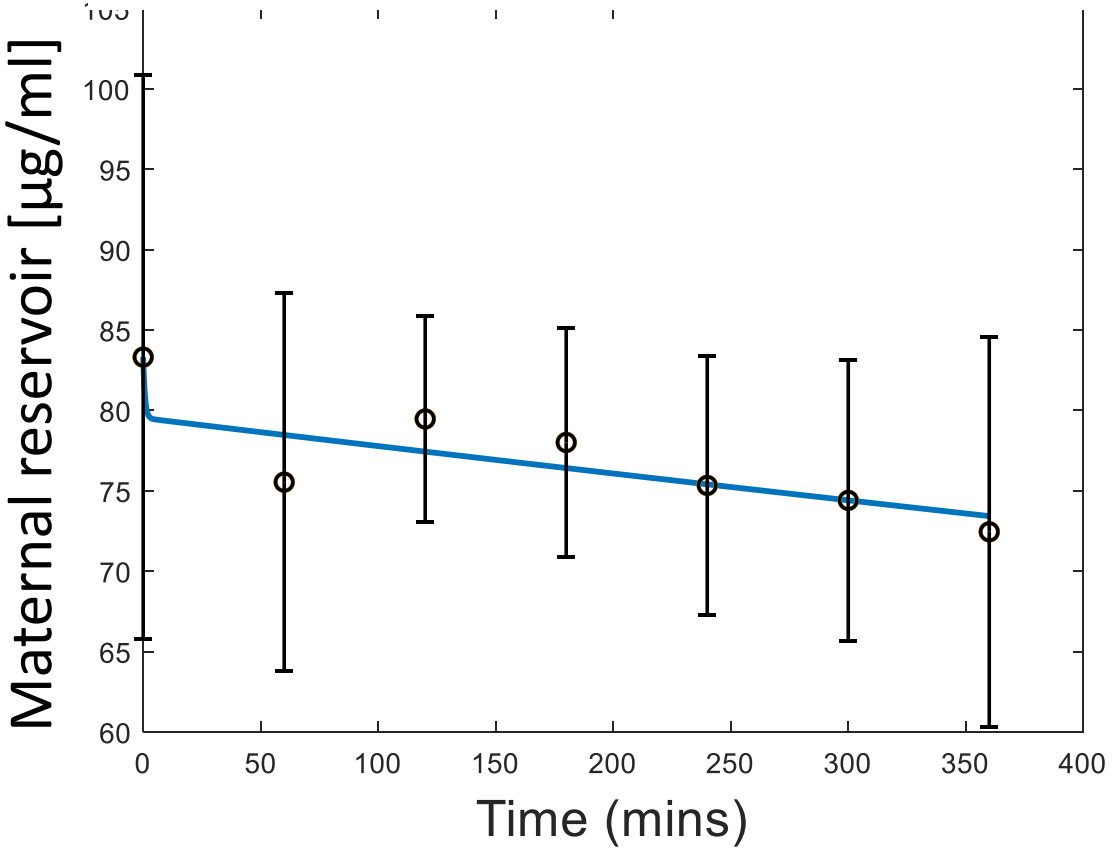
	Syncytiotrophoblast	Cytotrophoblast	Endothelium
FCGR1A	0.052682389	0.050611394	0.0230091
FCGR2A	0.116451473	0.175548568	0.7040963
FCGR3A	0.033640601	0.043945845	0.1061454
FCGR3B	0.001222741	0.001251652	0.0000000
FCGR2B	0.031548225	0.052579972	3.3019641
FCGRT (FcRn)	0.213283070	0.272239532	1.3797680

Afshar, Y. et al (2024) American Journal of Obstetrics and Gynecology, 230, 443.e1-443.e18

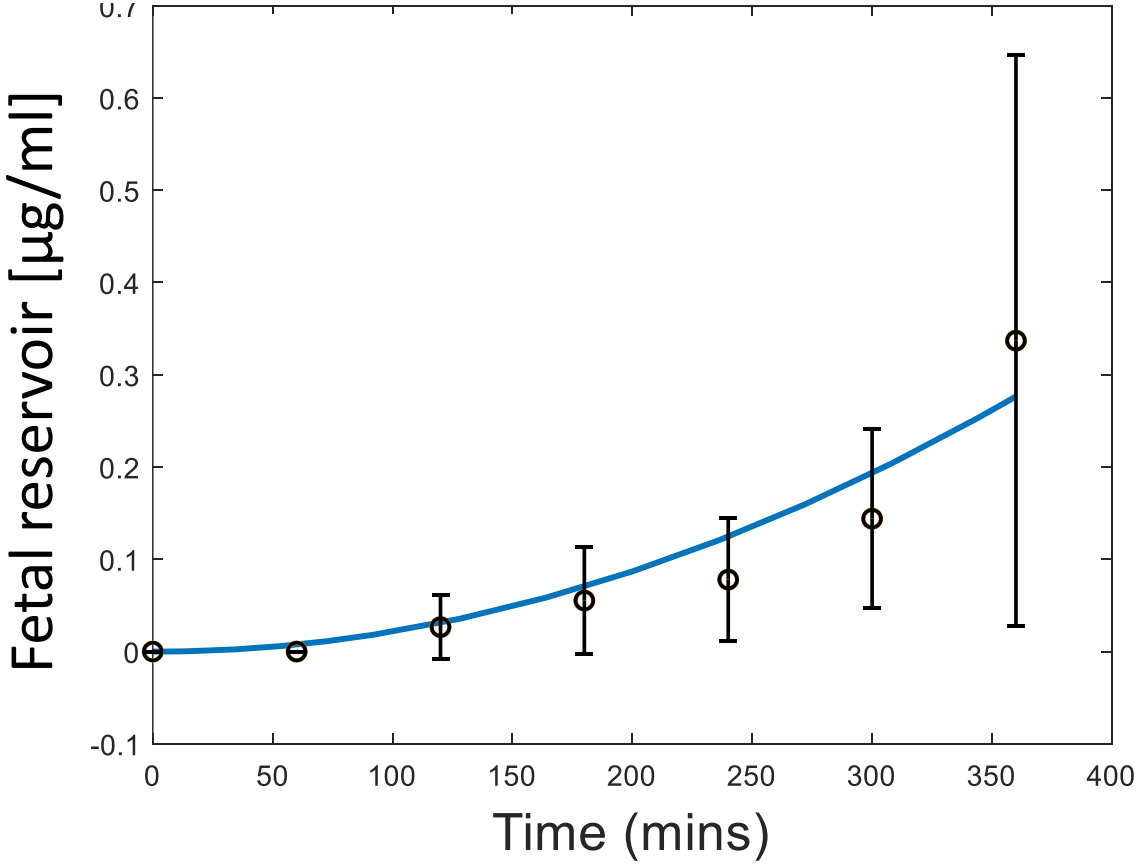
Infliximab transfer in the perfused placenta

Data from Eliesen et al (2020) Clin Pharmacol Ther. 2020 Jul;108(1):99-106.

Clearance from maternal circulation

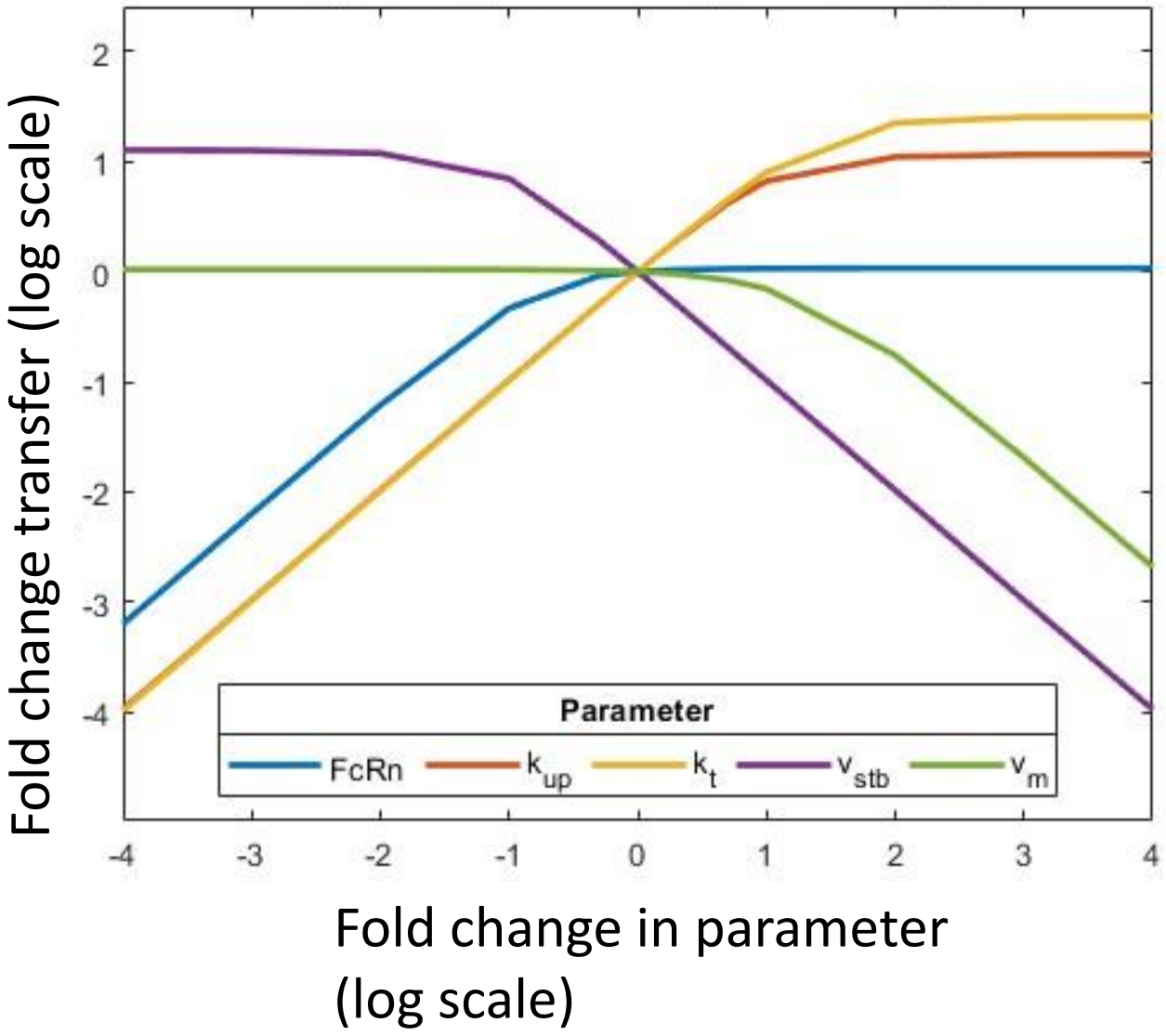


Appearance in circulation



➢ Transfer very slow compared to small molecules

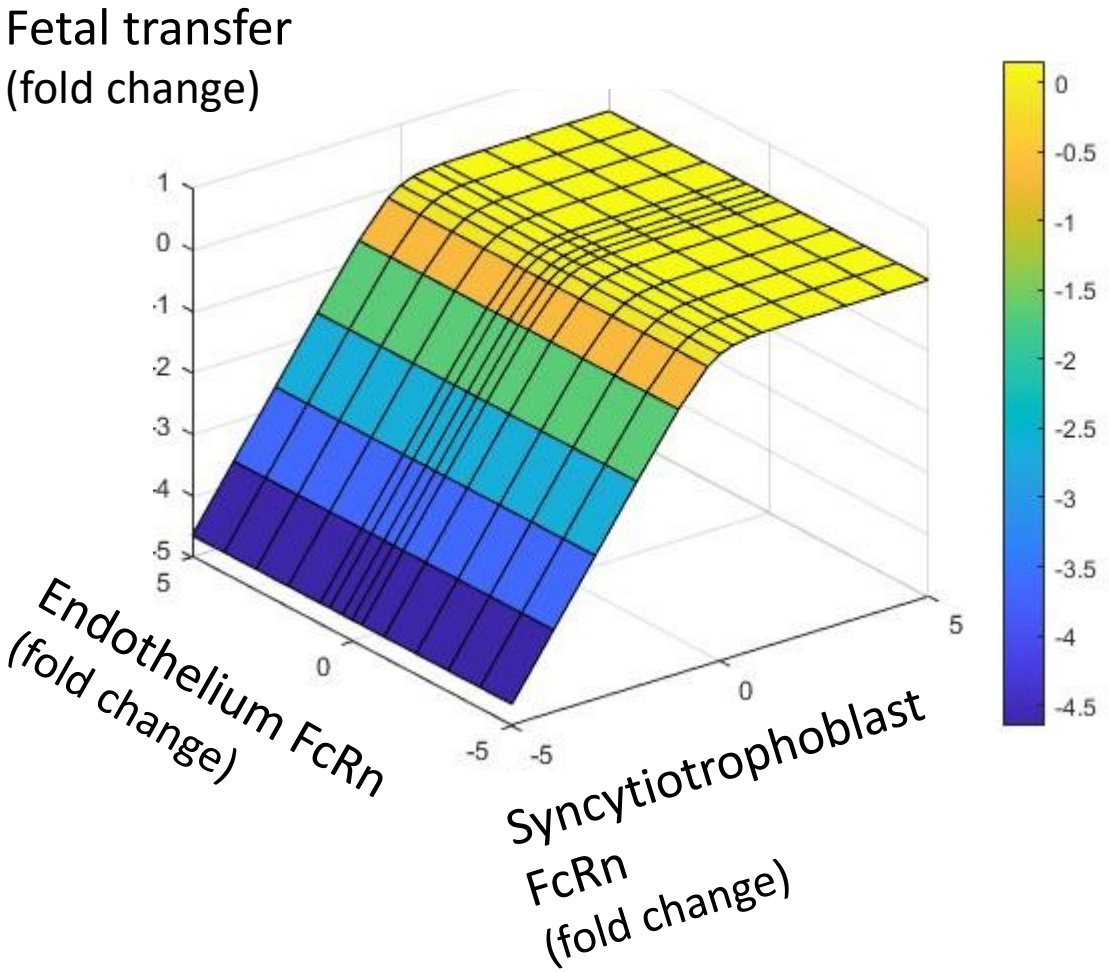
Sensitivity analysis
Identifying rate limiting processes

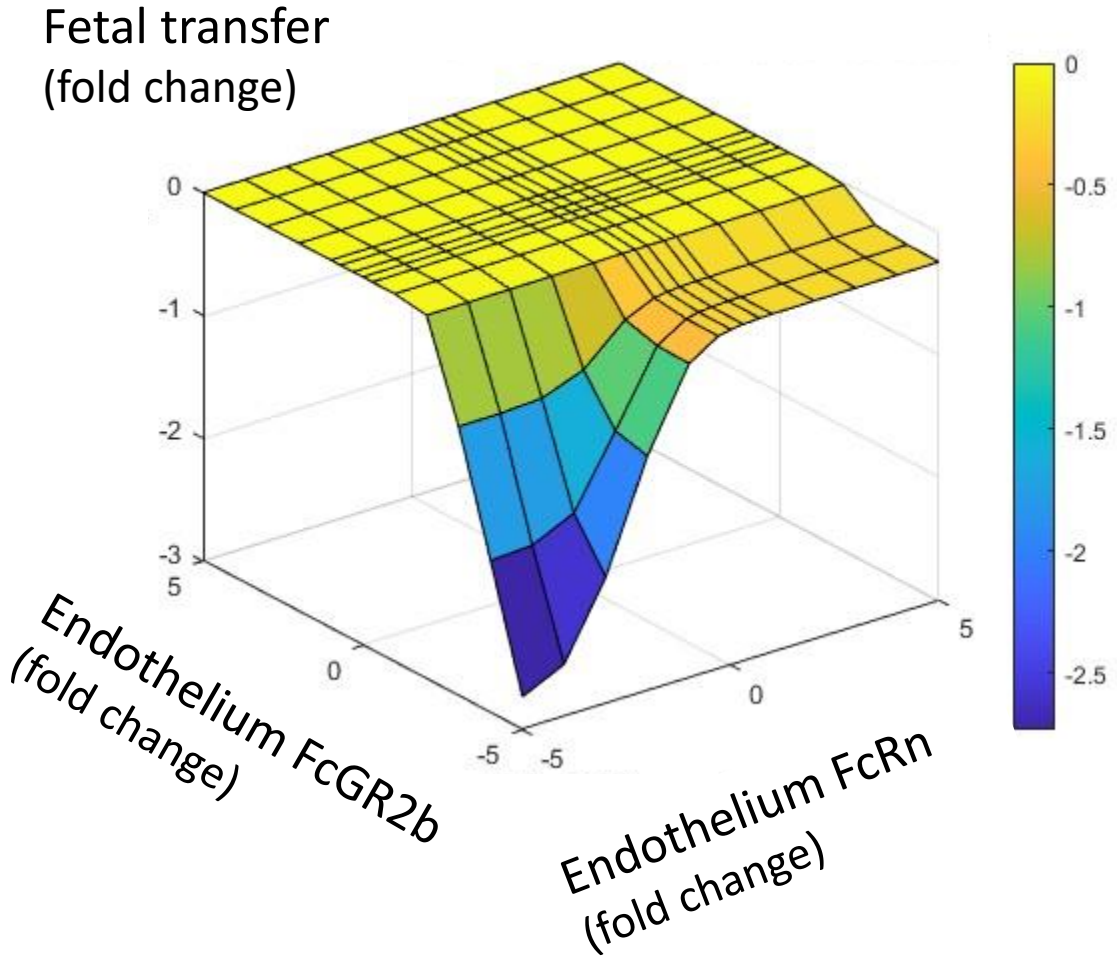


Five key parameters:

- FcRn concentration in the STB.
- Uptake rate from the IVS into the STB (k_{up})
- Transcytosis rate from the STB to the fetal capillaries (k_t)
- STB volume (V_{stb})
- IVS volume (V_m)

Sensitivity analysis to study interactions





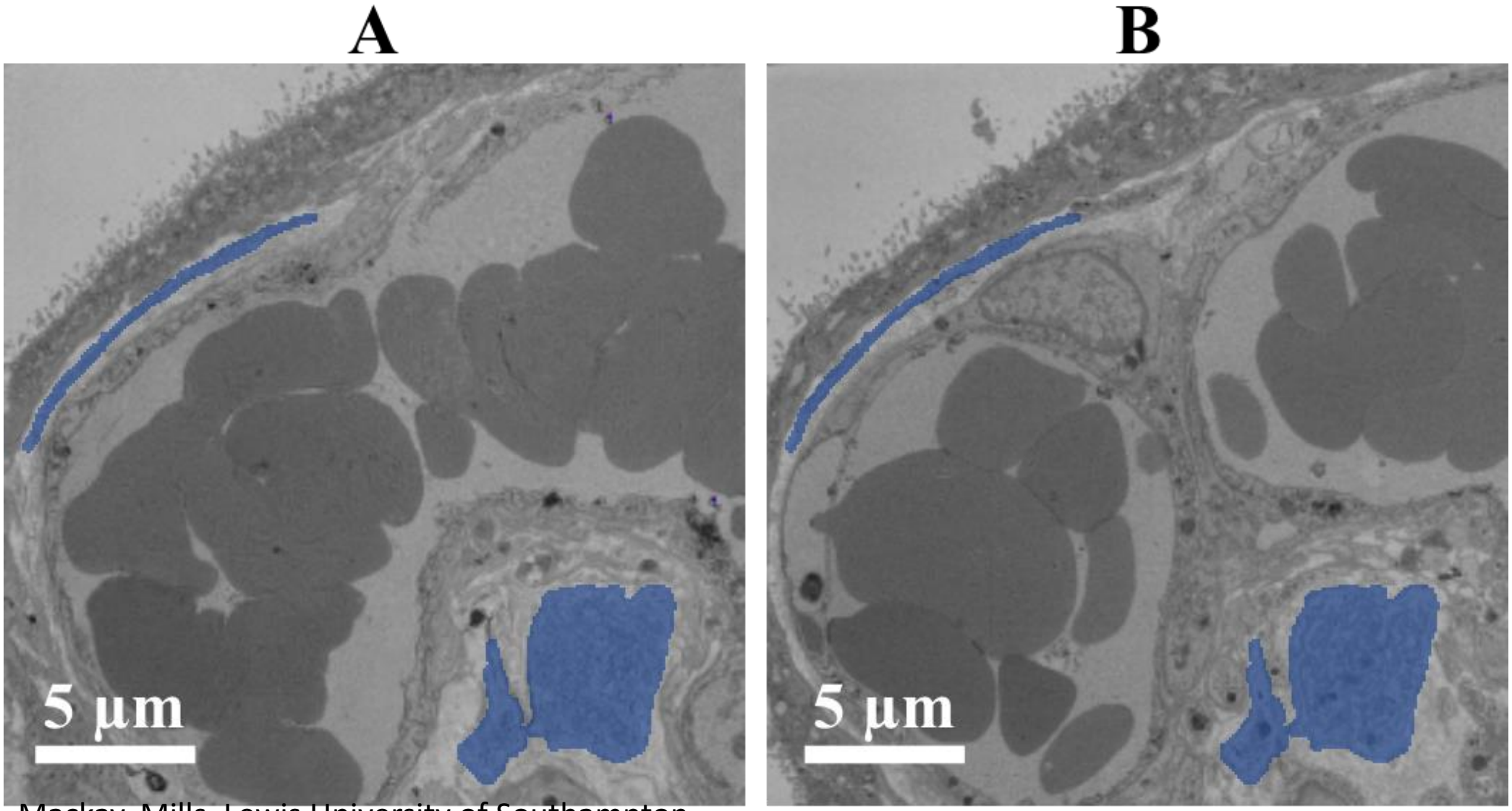
What we gain from modelling

- Check our understanding of the biology of transfer
- Understanding the experimental system
  - Human, animal, flow cell, organoid ….
- Once we have tested a model we can predict how clinical conditions affect transfer

Can machine leaning predict placental transfer?

Machine learning is very powerful

Can you tell which of these TEM images is fake?



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Machine learning and placental transfer

- Predicting placental transfer? - Not quite yet
  - To make models transferable between sites, patient groups etc. massive amounts of training data is required
  - The back box of current models means we can't check if they are predicting on something meaningful
- Where it might be useful now
  - Predicting novel drug receptor or transporter interactions
- But people are working in this area, so watch this space
  - Gomatam and Coutinho 2024, "A chirality-sensitive approach to predict chemical transfer across the human placental barrier" Toxicol Lett 394:66-75
  - Nigam et al. 2024 "Distinguishing Molecular Properties of OAT, OATP, and MRP Drug Substrates by Machine Learning". Parmaceutics ;16(5):592.

Conclusions

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- In silico is good for
  - Understanding the biology better
  - Understanding data from experimental systems better
  - Designing better experiments
- In silico is not good for
  - Replacing actual data!
- How can in silico help assessing risks?
  - Improving the design and interpretation of experiments
  - By simulating multiple maternal and placental states to predict where atypical transfer may occur

Acknowledgements

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- Bram Sengers
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