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Integrative Life-Stage Physiologically Based Pharmacokinetic (PBPK) and Thyroid Hormones Kinetics Model for In Vitro to In Vivo (IVIVE) Extrapolation of Thyroid High-Throughput (HTP) Assays

Clara Bay[1], Mary Gilbert[2], and Hisham El-Masri[2]

[1]ORISE, [2]USEPA, RTP, North Carolina

bay.clara@epa.gov

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Introduction

- Adequate levels of thyroid hormone (TH) are needed for proper fetal and early life stage brain development.
- Exposure to thyroid disrupting chemicals (TDCs) can lead to deficiencies of serum THs during pregnancy, depriving the fetal brain of hormone and compromising neurodevelopment.
- High throughput (HTP) in vitro assays of several biochemical pathways of thyroid hormone synthesis and metabolism are used to screen chemicals for their potential to disrupt the thyroid axis.

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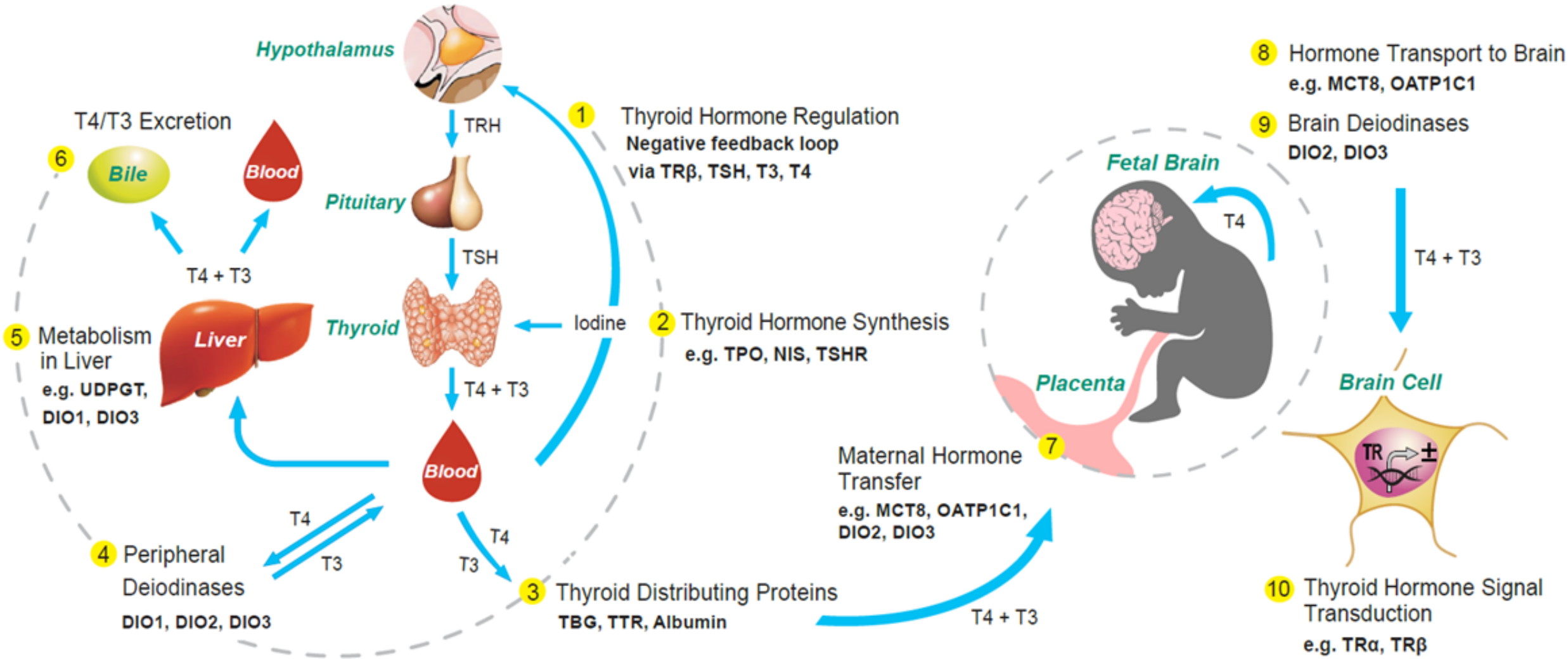
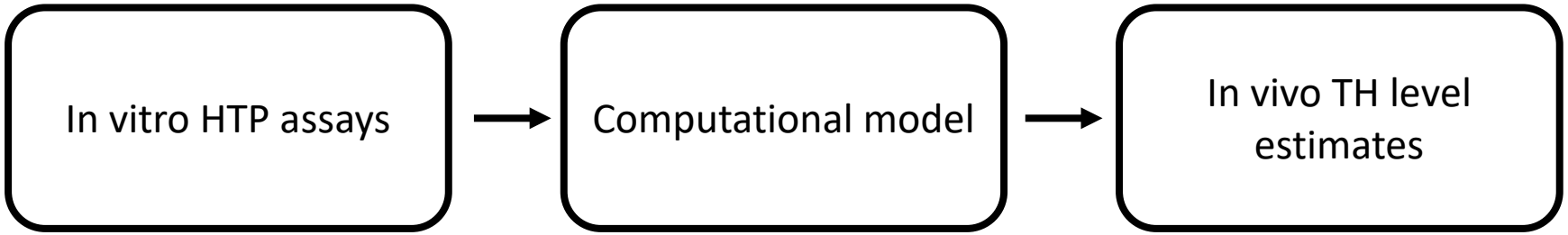
Sites of Interference for Thyroid Disrupting Chemicals



Gilbert et al., 2020, Endocrinology

Approach to answer question

- Created an integrative computational model
  - Life-stage physiologically based pharmacokinetic (PBPK) model
  - TH kinetic models
- Translates TH disruption in vitro high-throughput (HTP) assays to in vivo measures of circulating THs serum level in a pregnant mother, the fetus and the neonate.



Integrative Model Components

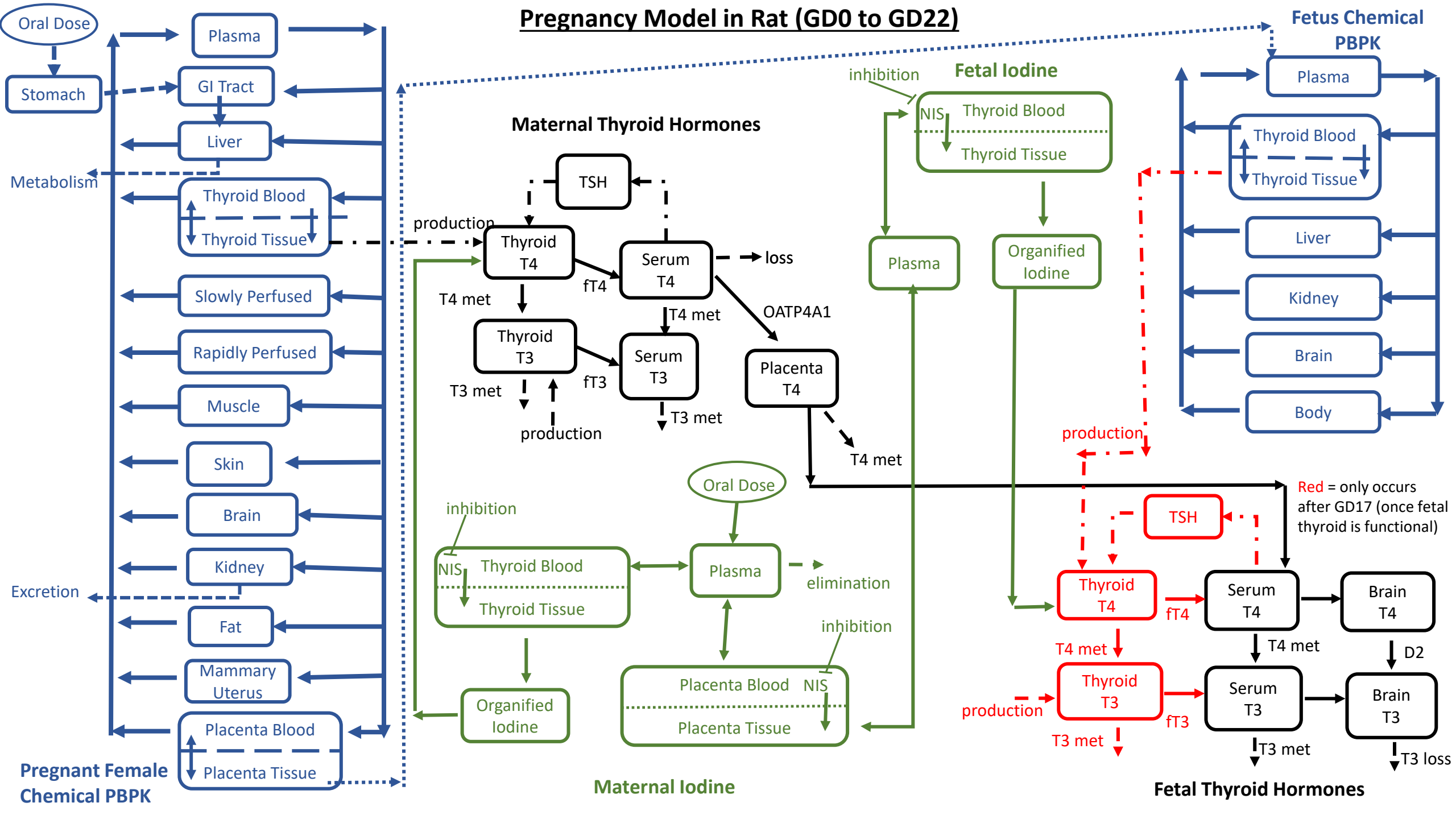
- Pregnancy model in rats
  - Follows dam and fetus throughout pregnancy (GD 0 to GD 22)
  - Follows mother and pup after birth (birth and on)
- Chemical PBPK model
  - Oral dose of a potential TDC
- TH kinetics model
  - T4 production impacted by TDC concentration in thyroid
  - T3/T4 followed in serum, thyroid, placenta, fetal/pup brain
- Iodine kinetics model
  - Daily dietary iodine dose.
  - Transformed to organified iodine, which forms T4 in the thyroid.

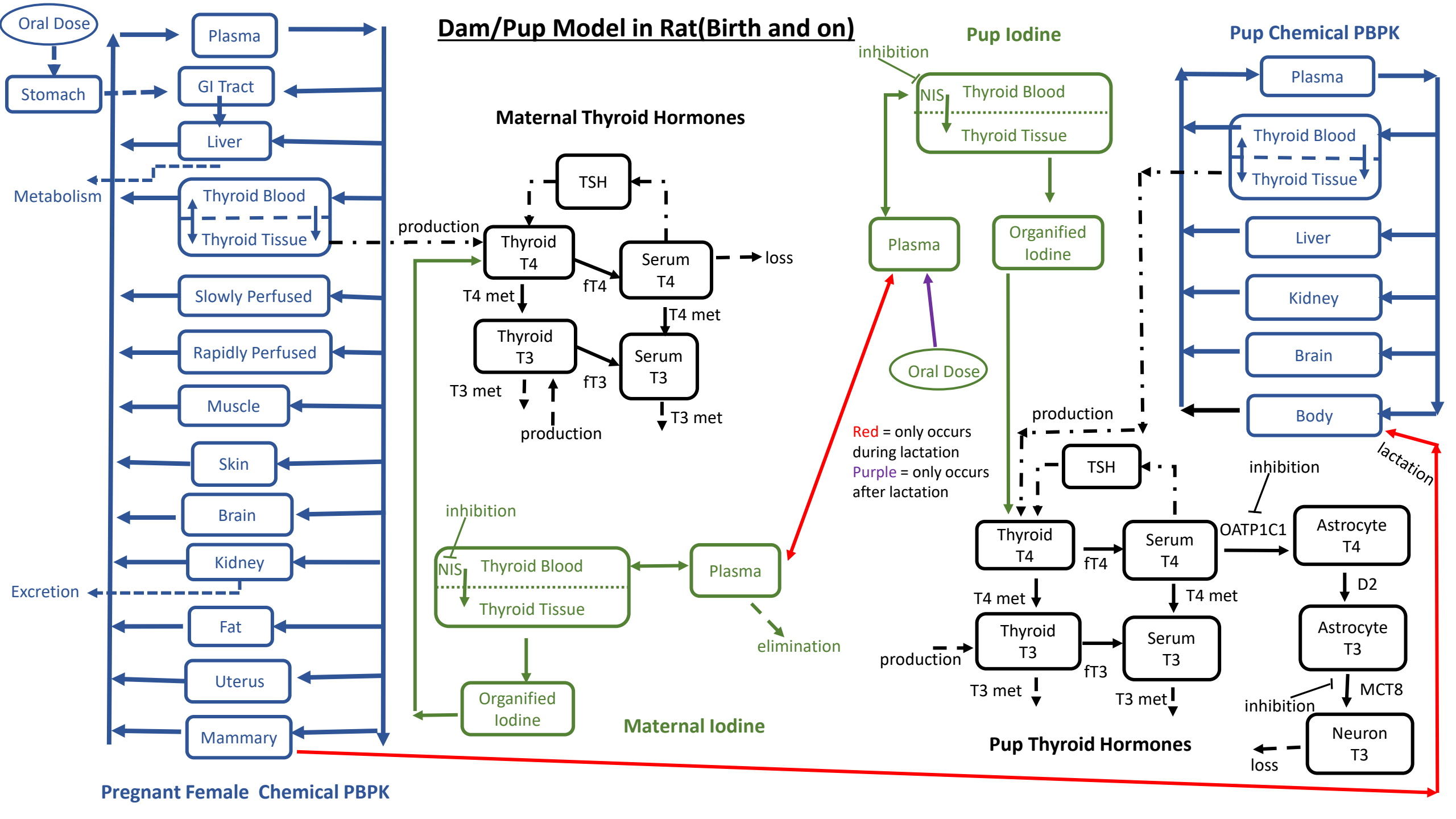
- Differences in model during pregnancy/after birth

During pregnancy	After Birth
Transport across placenta of TDC, T4, iodine.	TDC and iodine transported to pup via lactation. Oral dose of iodine after.
Fetal TH production only after GD 17.	Pup produces own TH.
Tracks T4 and T3 in whole brain in fetus.	Tracks T4/T3 in astrocytes and T3 in neurons of pup brain.

- Transporters and enzymes included in model

Transporters and enzymes	Function
TPO	Involved in TH production. Inhibition by TDC included.
NIS	Iodine transport into tissue. Inhibition by TDC included.
OATP4A1	T4 transport across the placenta.
OATP1C1	Blood to brain transport of T4. Inhibition term included.
MCT8	Astrocyte to neuron transport of T3. Inhibition term included.
D2	T4 to T3 transformation in the brain.


Pregnancy Model in Rat (GD0 to GD22)
Oral Dose
Stomach
Plasma
GI Tract
Liver
Metabolism
Thyroid Blood
Thyroid Tissue
Slowly Perfused
Rapidly Perfused
Muscle
Skin
Brain
Kidney
Excretion
Fat
Mammary
Uterus
Placenta Blood
Placenta Tissue
Pregnant Female
Chemical PBPK
Maternal Thyroid Hormones
TSH
production
Thyroid
T4
Serum
T4
loss
fT4
T4 met
Thyroid
T3
Serum
T3
fT3
T3 met
production
T4 met
OATP4A1
Placenta
T4
T4 met
Oral Dose
inhibition
NIS
Thyroid Blood
Thyroid Tissue
Plasma
elimination
inhibition
Placenta Blood
NIS
Placenta Tissue
Organified
Iodine
Maternal Iodine
inhibition
Fetal Iodine
NIS
Thyroid Blood
Thyroid Tissue
Plasma
Organified
Iodine
Fetus Chemical
PBPK
Plasma
Thyroid Blood
Thyroid Tissue
Liver
Kidney
Brain
Body
production
Red = only occurs
after GD17 (once fetal
thyroid is functional)
TSH
Thyroid
T4
fT4
Serum
T4
Brain
T4
T4 met
D2
T4 met
production
Thyroid
T3
fT3
Serum
T3
Brain
T3
T3 met
T3 met
T3 loss
Fetal Thyroid Hormones


Dam/Pup Model in Rat(Birth and on)
Oral Dose
Stomach
Plasma
GI Tract
Liver
Metabolism
Thyroid Blood
Thyroid Tissue
Slowly Perfused
Rapidly Perfused
Muscle
Skin
Brain
Kidney
Excretion
Fat
Uterus
Mammary
Pregnant Female Chemical PBPK
Maternal Thyroid Hormones
TSH
production
Thyroid T4
Serum T4
loss
fT4
T4 met
Thyroid T3
Serum T3
fT3
T3 met
production
T4 met
T3 met
inhibition
NIS
Thyroid Blood
Thyroid Tissue
Plasma
elimination
Organified Iodine
Maternal Iodine
Pup Iodine
inhibition
NIS
Thyroid Blood
Thyroid Tissue
Plasma
Organified Iodine
Oral Dose
Red = only occurs during lactation
Purple = only occurs after lactation
Pup Chemical PBPK
Plasma
Thyroid Blood
Thyroid Tissue
Liver
Kidney
Brain
Body
lactation
production
TSH
Thyroid T4
Serum T4
fT4
T4 met
Thyroid T3
Serum T3
fT3
T3 met
production
T4 met
T3 met
inhibition
OATP1C1
Astrocyte T4
D2
Astrocyte T3
MCT8
inhibition
Neuron T3
loss
Pup Thyroid Hormones

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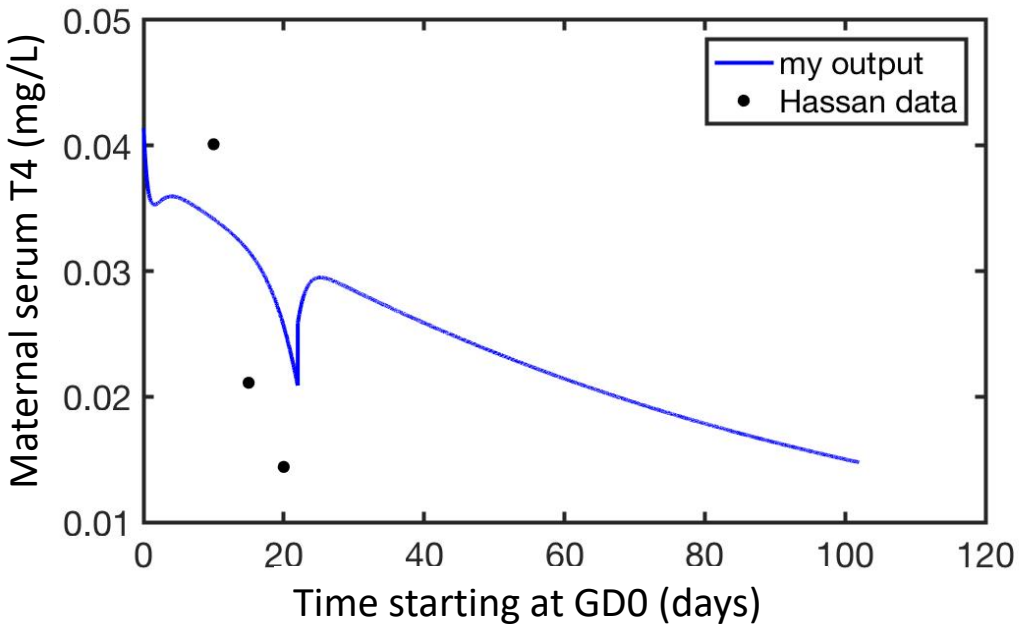
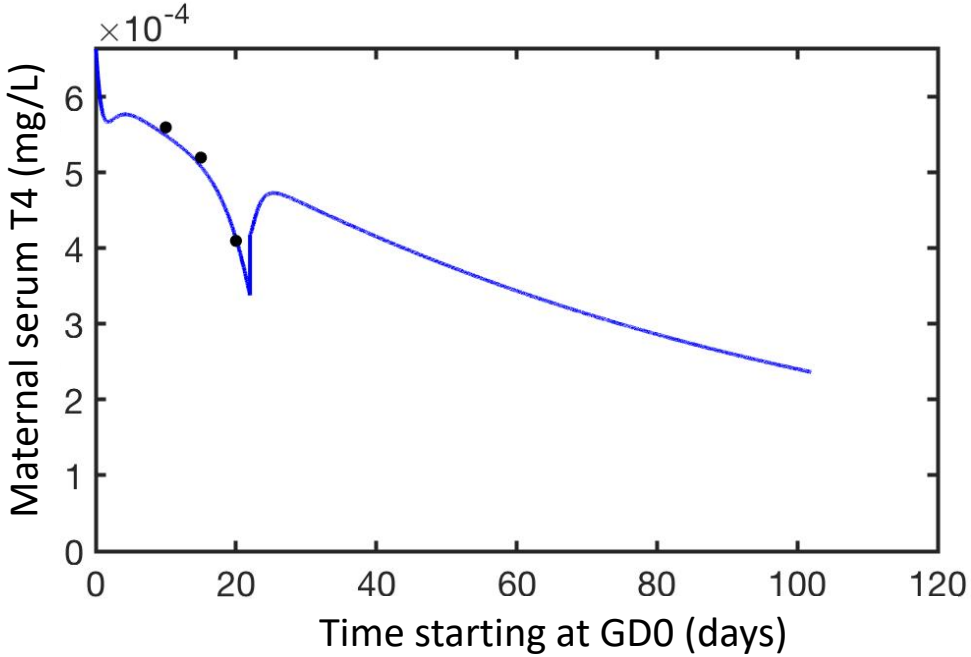
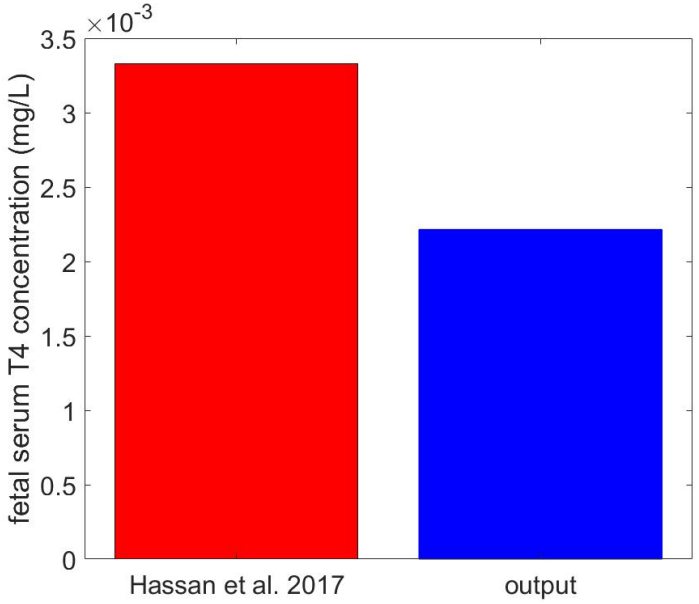
Results

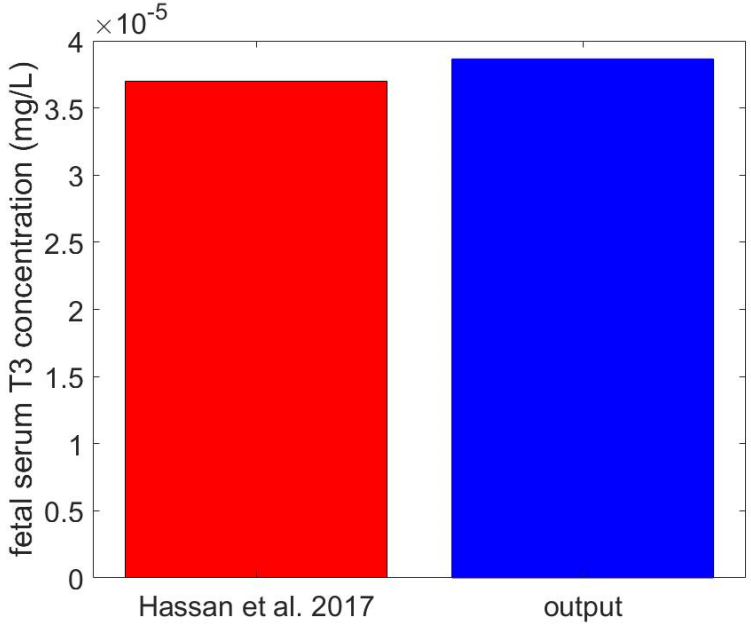
- Comparing output, under normal conditions, to published data.
- Calibrating the model using different doses of TDC (in these examples, PTU) and iodine.
- ‘Normal’ iodine intake set as 4.5 ug/day.
- Chemical inhibition of OATP1C1 and MCT8 transporters was only considered in the pup developing brain.

Simulated dam and fetal T3/T4 in serum, no chemical

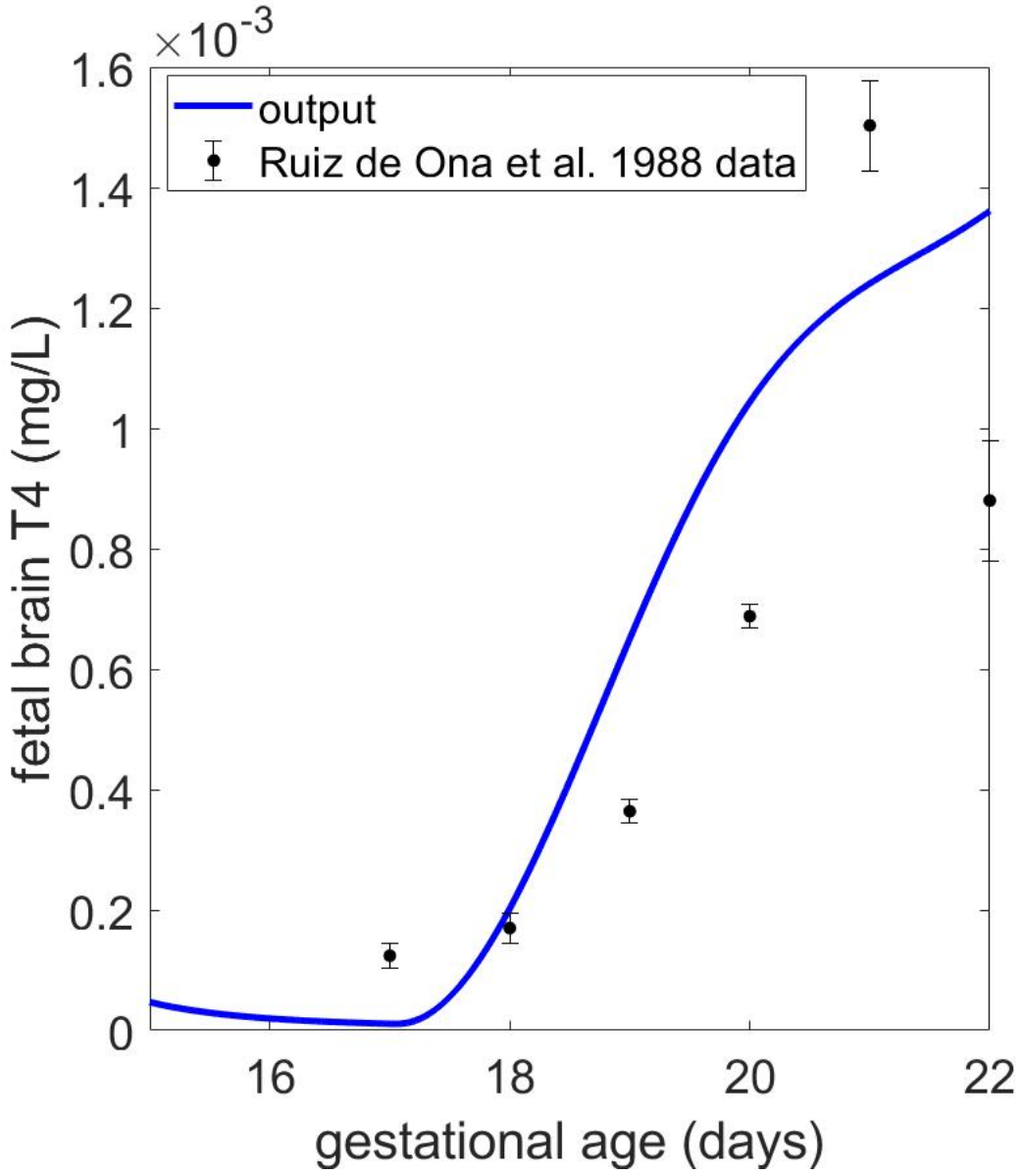


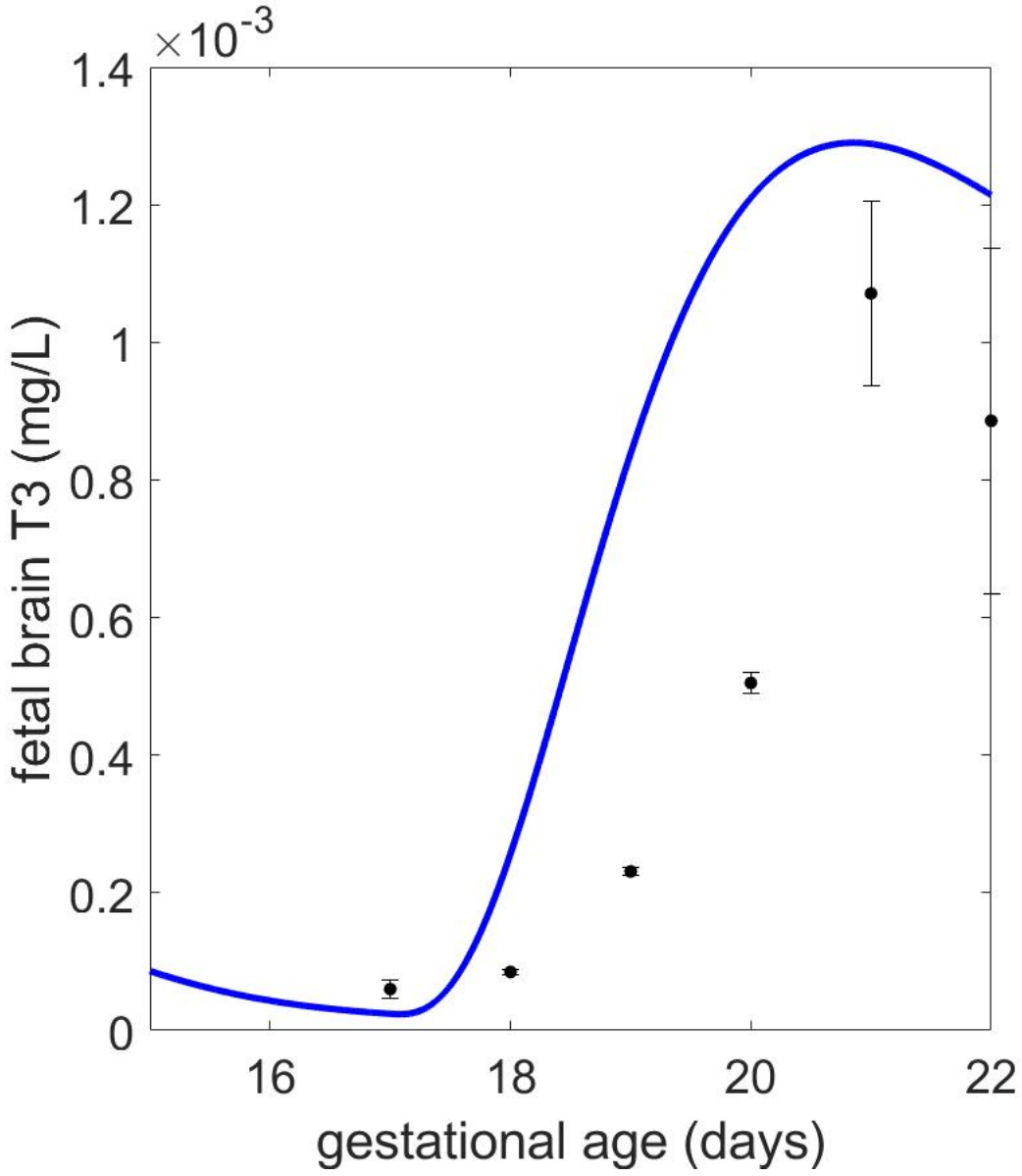




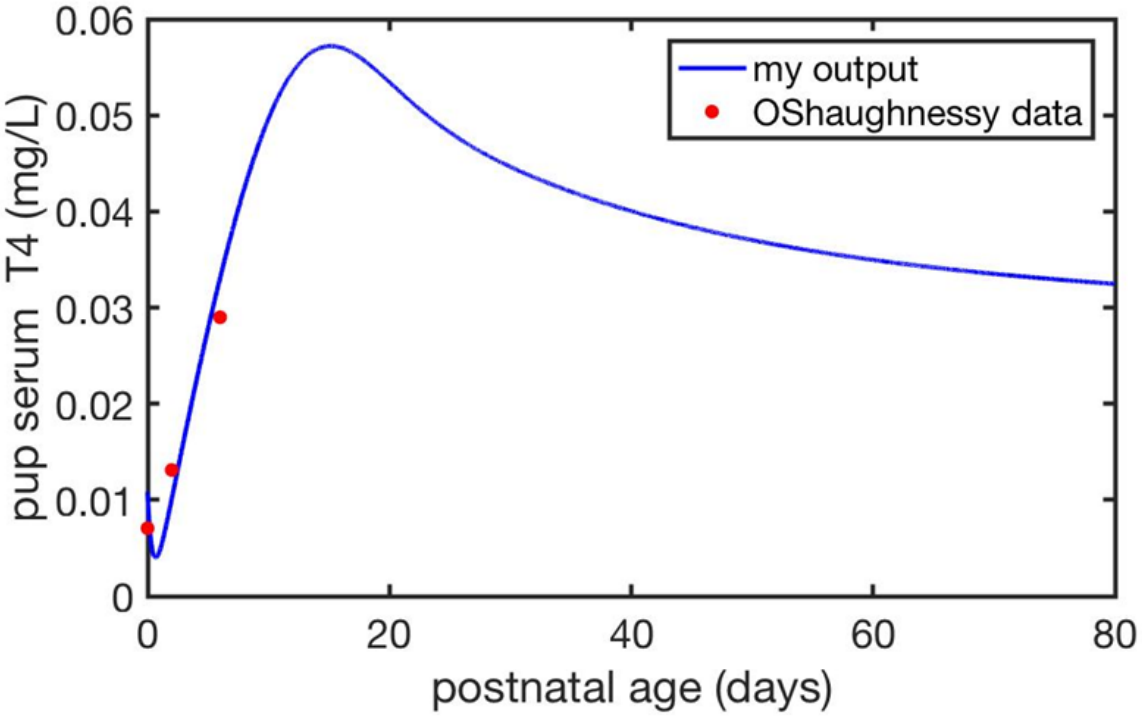


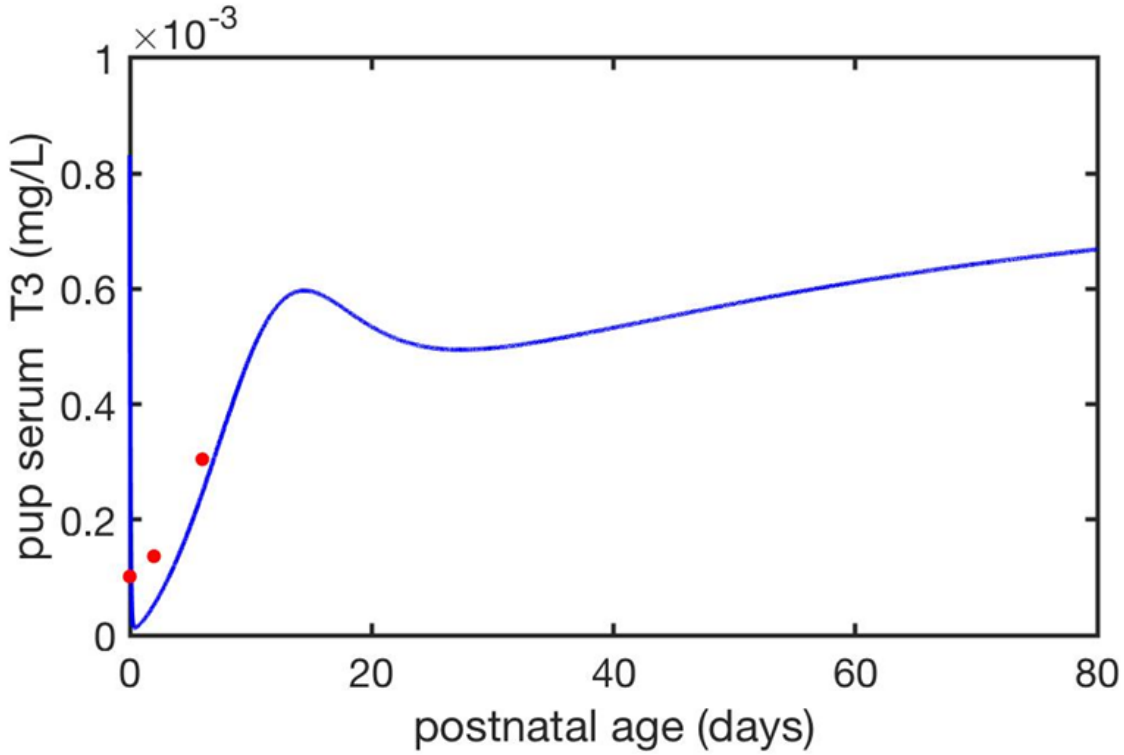
Simulated Fetal Brain T3/T4, no chemical





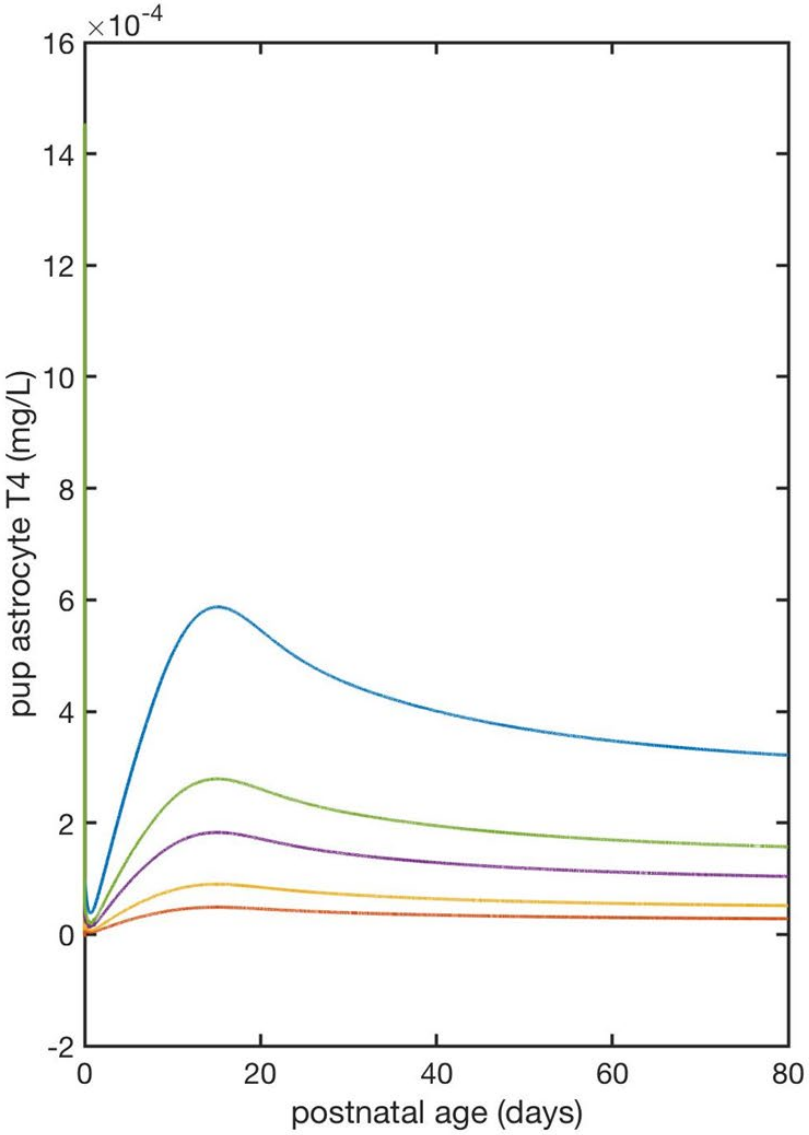
Simulated Pup T3/T4 in serum, no chemical

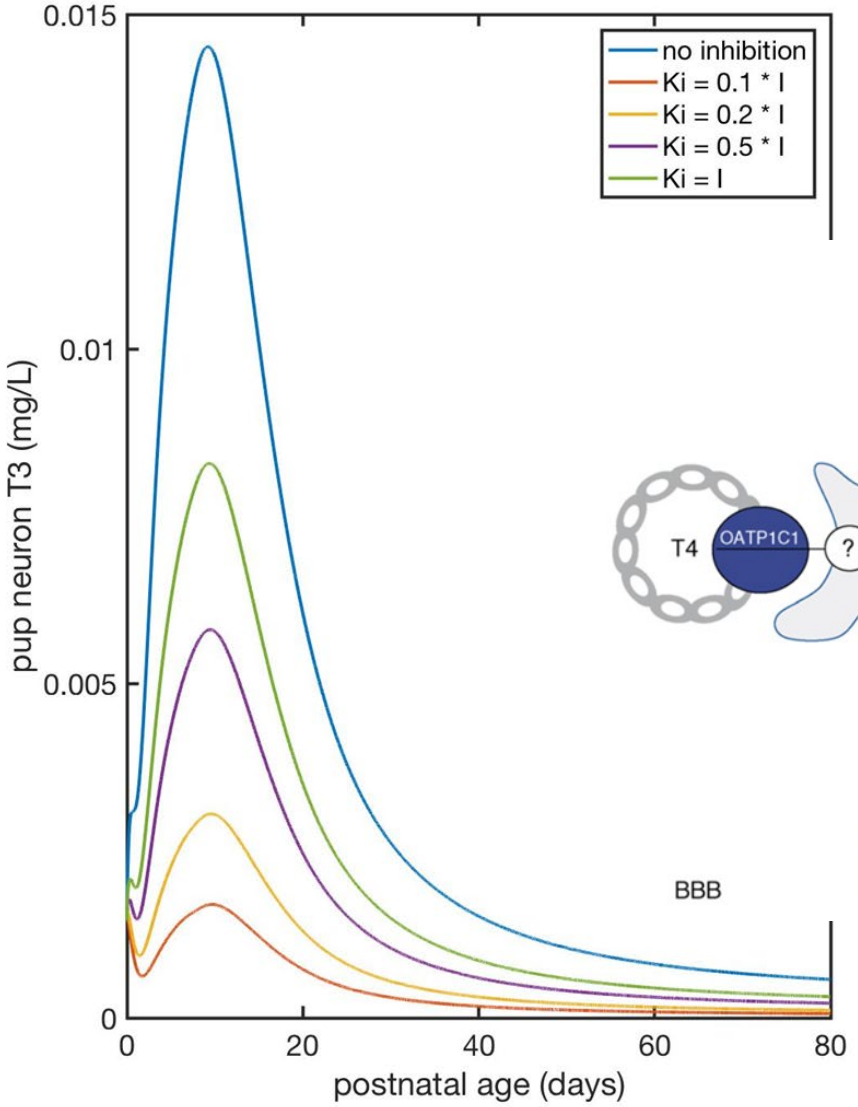


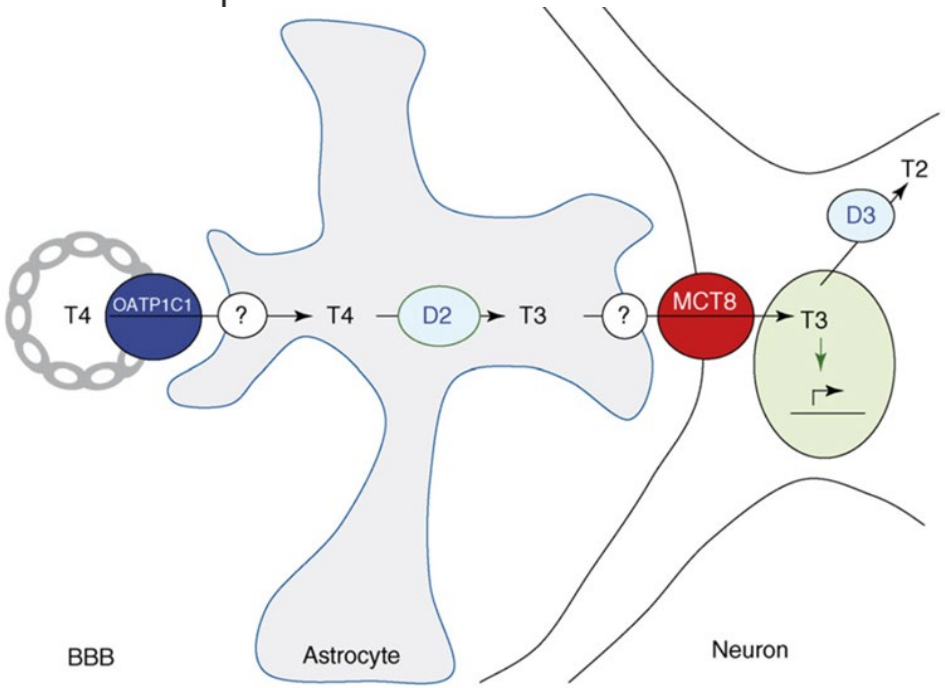


O'Shaughnessy et al., 2019, Sci Rep.

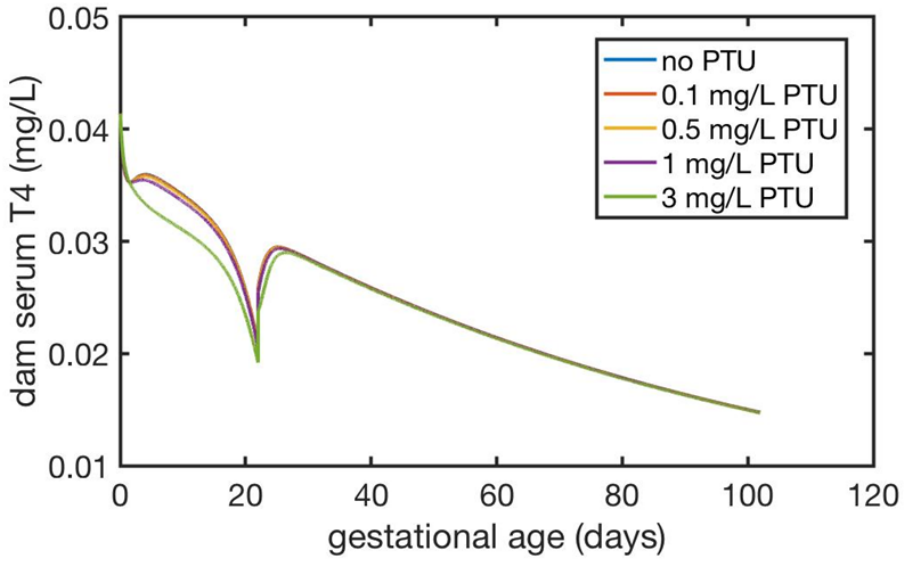
Simulated Pup Brain TH with transporter inhibition

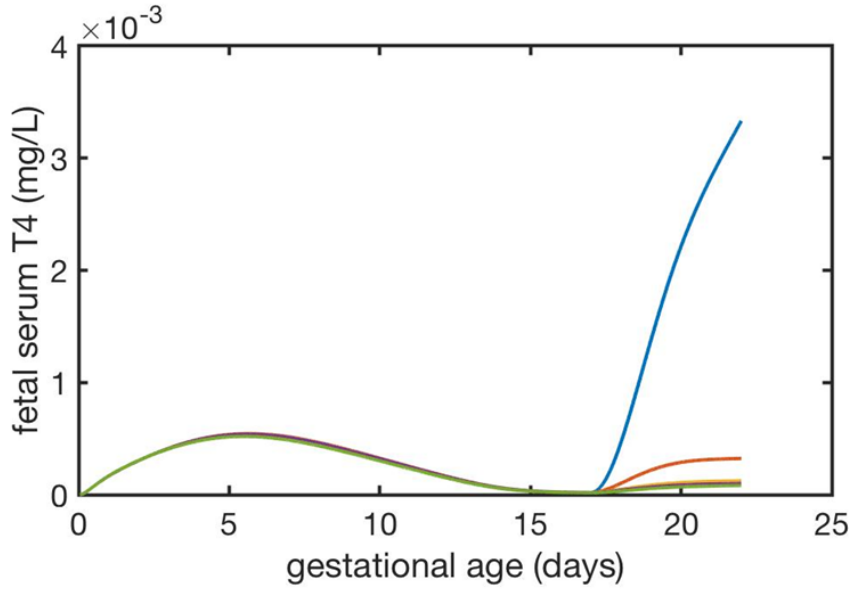


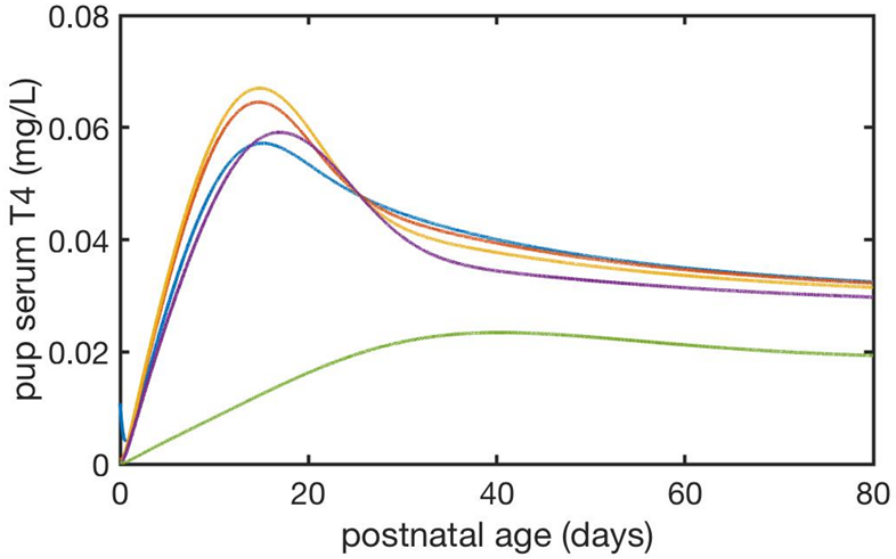


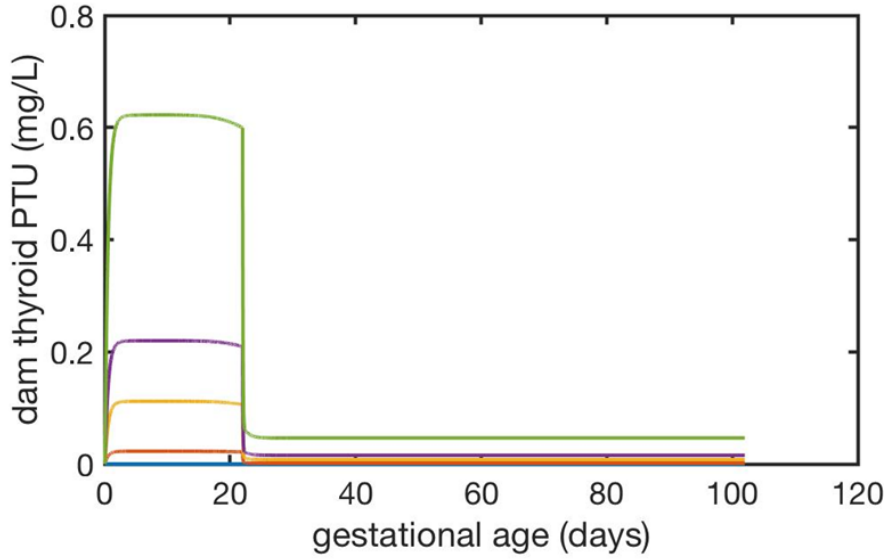


Simulations comparing PTU doses









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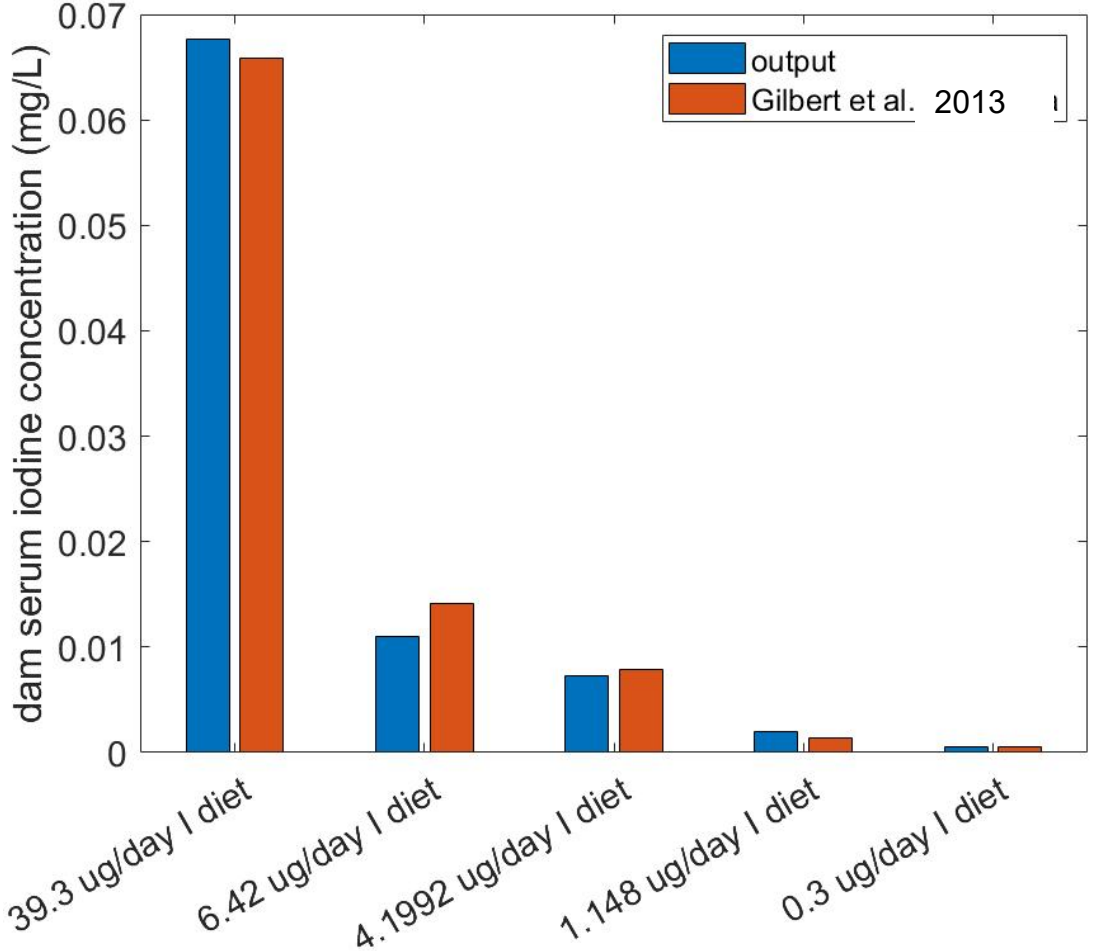
PN 21



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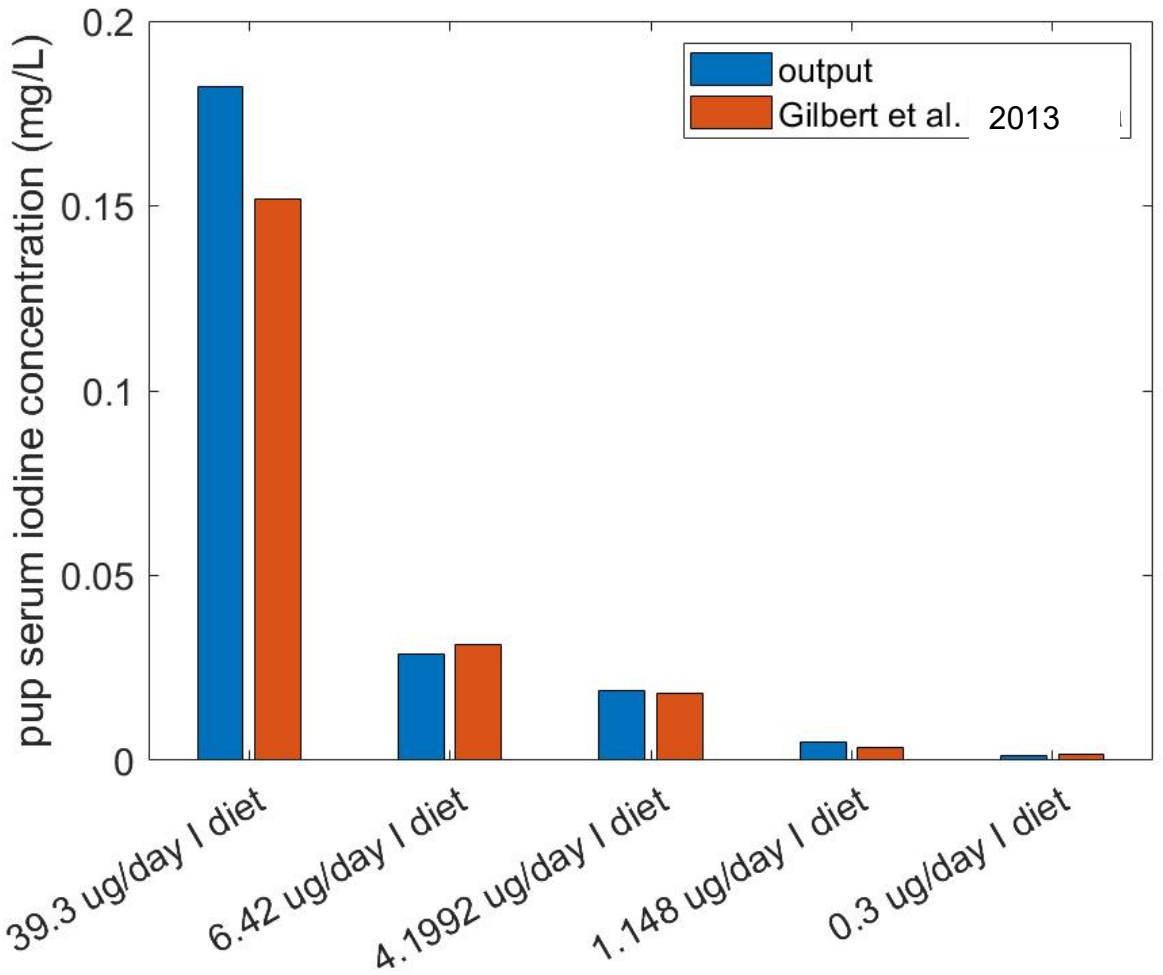
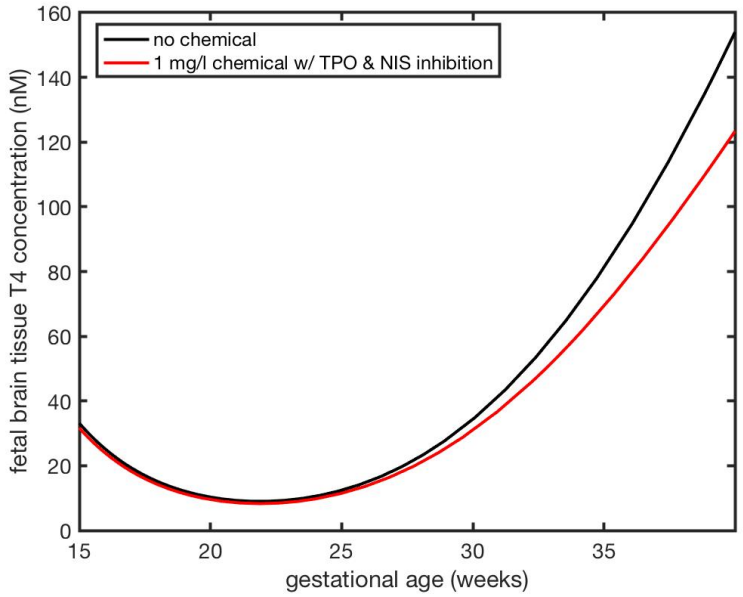
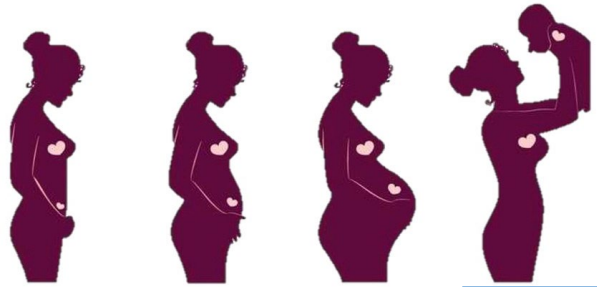
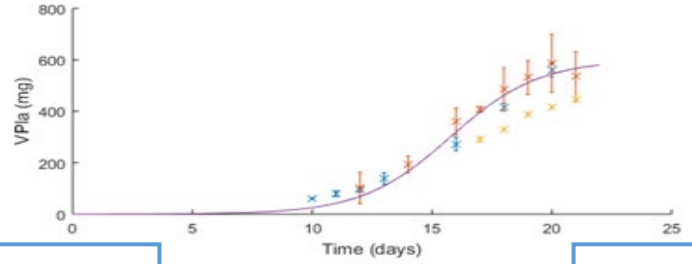


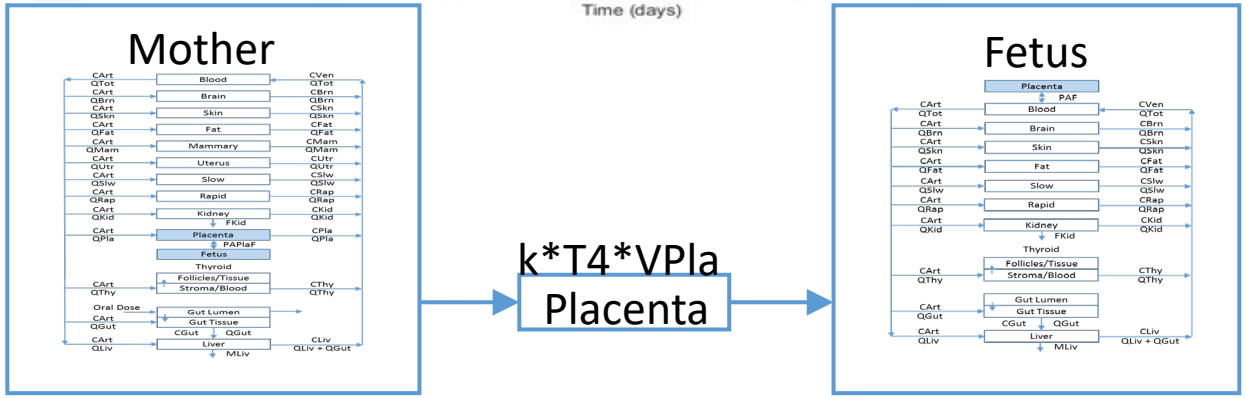
Iodine levels given different intake levels

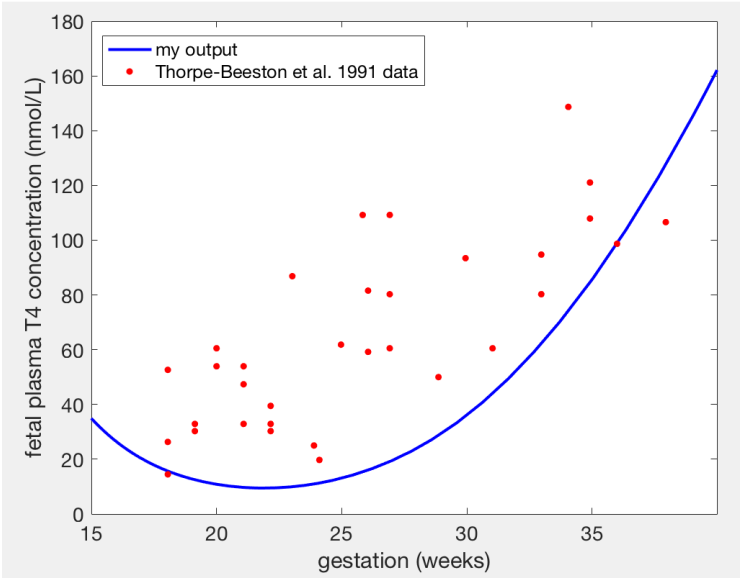
Human Life-Stage TH Kinetics Modeling

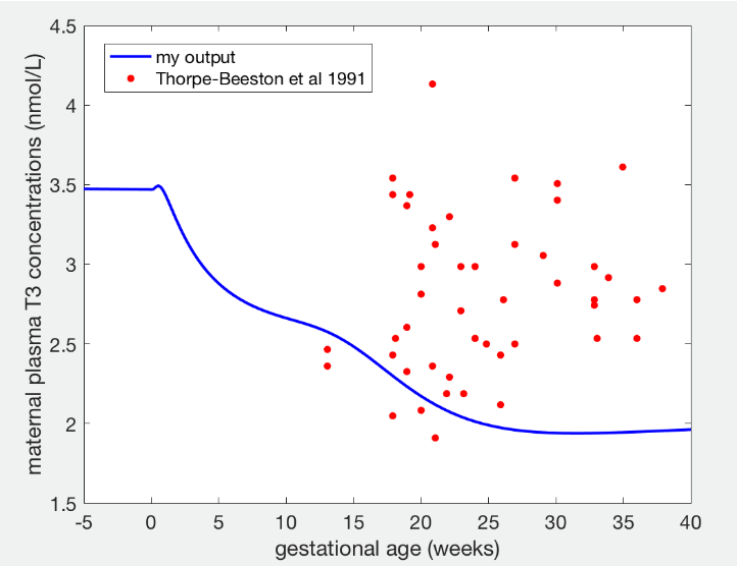












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Conclusions

- Computational methods are useful in assessing the integrative impact of chemical and TH kinetics on circulating serum levels of the hormones, especially during pregnancy.
- Dose-response information from high throughput screening assays along the HPT axis can be used as inputs to the presented computational framework to estimate in vivo TH serum levels during pregnancy
- This integrative quantitative approach can be generalized across many chemicals and exposure scenarios to screen chemicals for their potential disruption of TH serum levels.