

A Hierarchical Bayesian Workflow for Clinical Endpoints in CNS Trials using HSSM

De-risking neuro-psychiatric drug development and clinical trials

The Problem

Approval rate in clinical trials for CNS drugs is less than half the non-CNS domain...



*Tufts CSDD Impact Report 2014

The Cause

Difficulty in quantifying treatment response; lack of mechanistic insights - treatments fail to act specifically on targeted brain mechanisms.

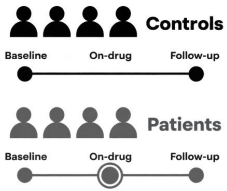


Our Approach

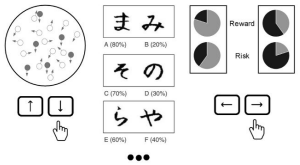
An **integrated computational analysis platform** for Identifying **mechanism-oriented "computational biomarkers"**.

Basic Analysis Pipeline

Population

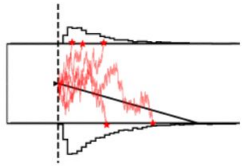


Level 1: Task Battery

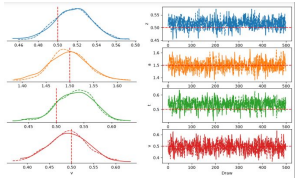


Task Design

Level 2: Computational Modeling

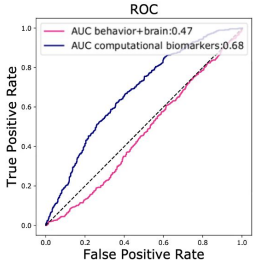


Level 3: Parameter Inference



Task Models

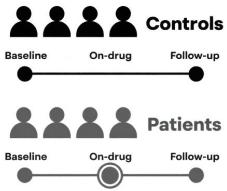
Level 4: Classification



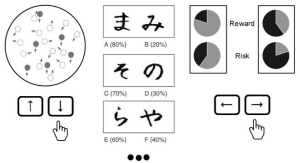
Prediction

Process Models help

Population

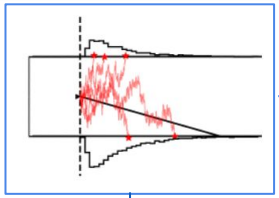


Level 1: Task Battery

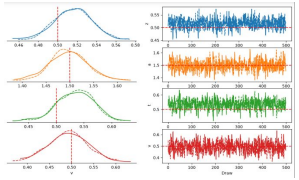


Task Design

Level 2: Computational Modeling

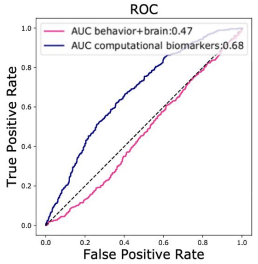


Level 3: Parameter Inference

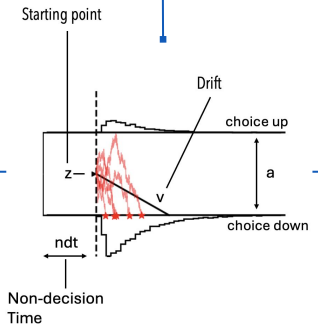


Task Models

Level 4: Classification



Prediction

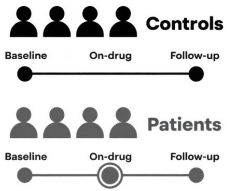


Choice/Reaction-Time

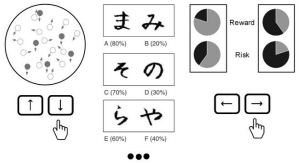
Mechanistic
Interpretable
Low Dimensional

Process Models help

Population

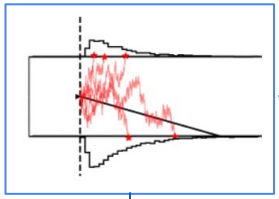


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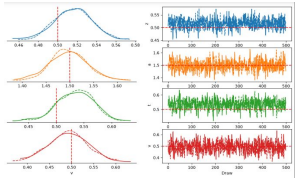


Task Design

Level 2: Computational Modeling

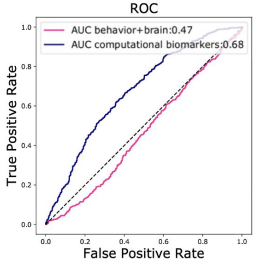


Level 3: Parameter Inference



Task Models

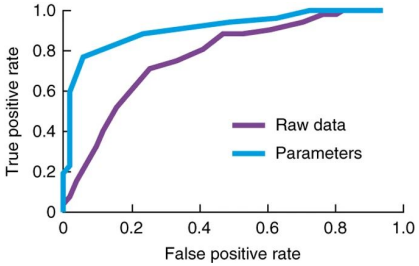
Level 4: Classification



Prediction

Applications across CNS disorder Spectrum:

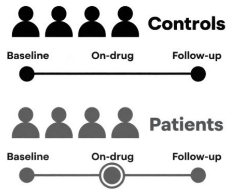
- Presymptomatic Huntington's
- Impulsivity in Parkinson's
- Schizophrenia
- Bipolar
- Depression
- ADHD
- ...



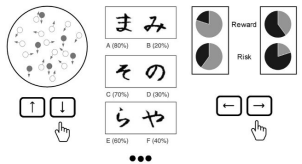
Core Claim 2: Many mechanisms to test

HSSM

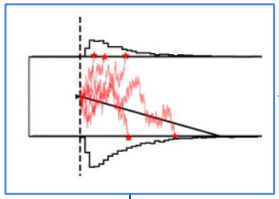
Population



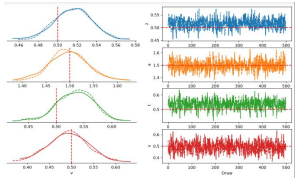
Level 1: Task Battery



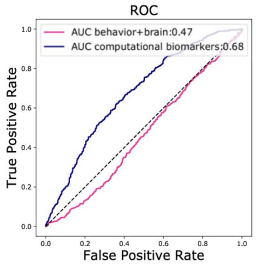
Level 2: Computational Modeling



Level 3: Parameter Inference



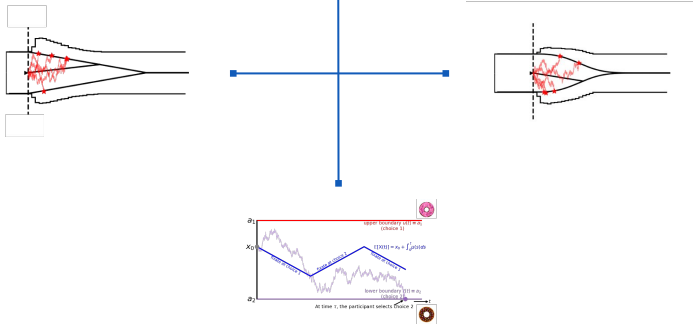
Level 4: Classification



Task Design

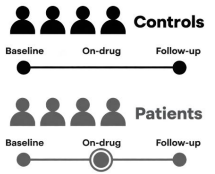
Task Models

Prediction

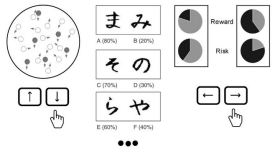


A plethora of **model variations** exist that extend the **landscape** of **candidate mechanisms / computational biomarkers**

Population

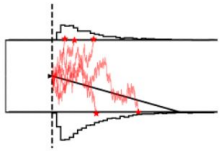


Level 1: Task Battery

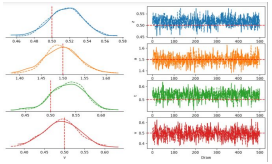


Task Design

Level 2: Computational Modeling

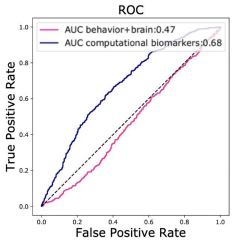


Level 3: Parameter Inference



Task Models

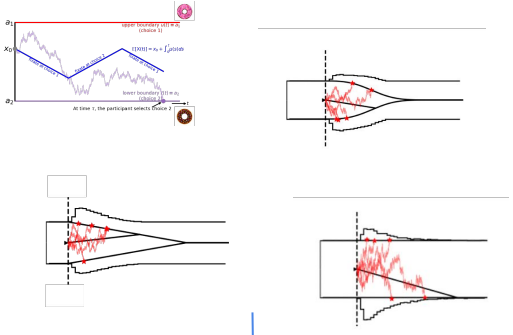
Level 4: Classification



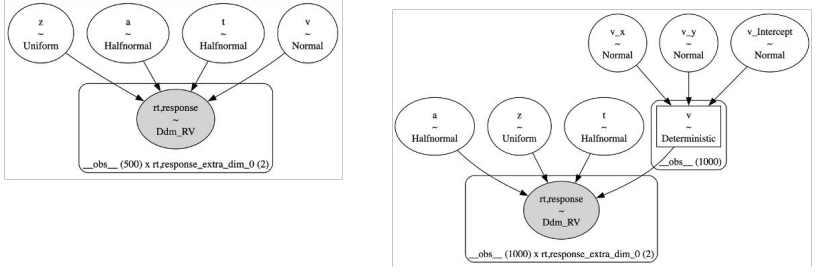
Prediction

HSSM Workflow Elements

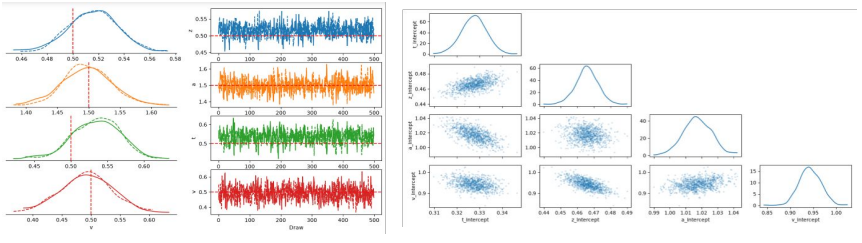
1. Choose your cognitive model



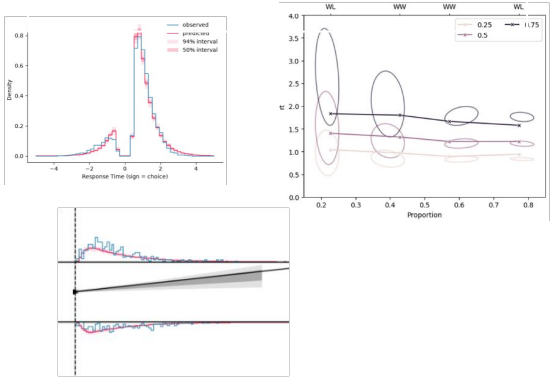
2. Build a graphical model around it



3. Infer parameters

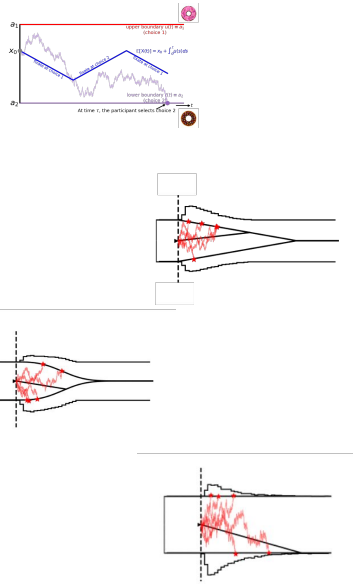


4. Analyze your fits



HSSM Workflow Elements

1. Choose your cognitive model



SSMS

LANS

Not all these models have analytical likelihoods.

We **support multiple mechanisms**,

1. Analytical
2. Numerical
3. ML-based surrogates

sbi

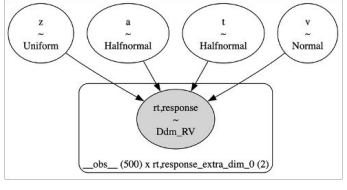
BayesFlow

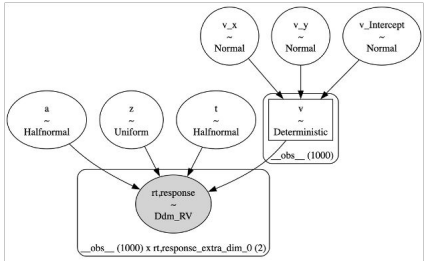
HSSM Workflow Elements

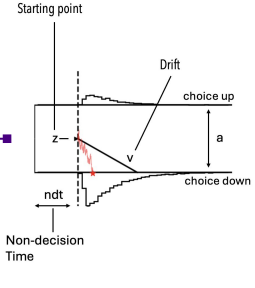
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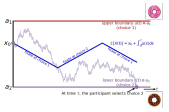
PyMC

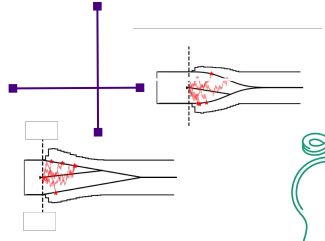
Bambi











Parameter-wise hierarchical regressions

Brain / Physiological measures enter as covariates

Processes on Parameters



TMS



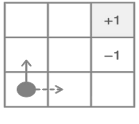
eye-tracking



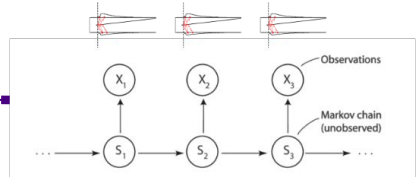
DBS



neural

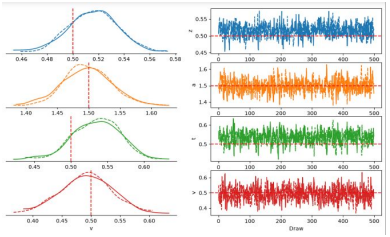


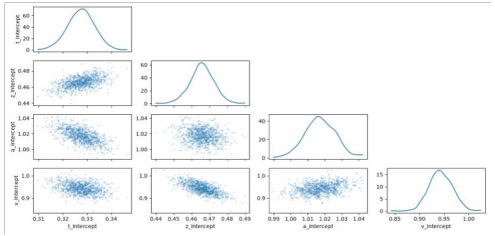
learning



HSSM embeds in the broader SBI ecosystem

3. Infer parameters





numpyro

MCMC

VI

MAP

MLE

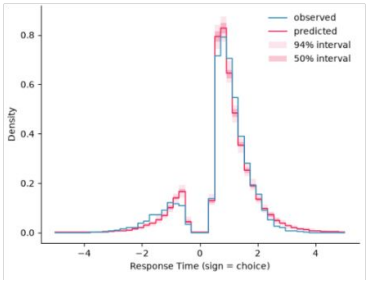
Compile model -> Use however you prefer

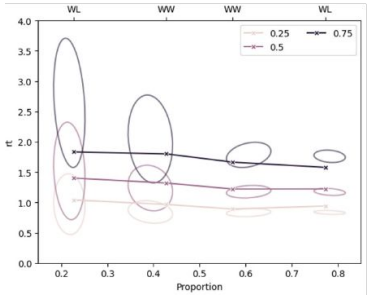
PyMC

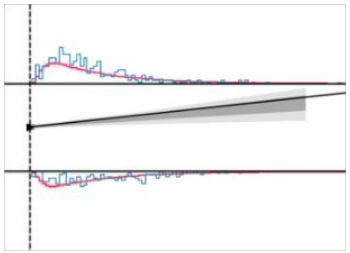
Nutpie

HSSM embeds in the broader SBI ecosystem

4. Analyze your fits







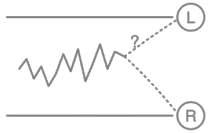
HSSM Proprietary:

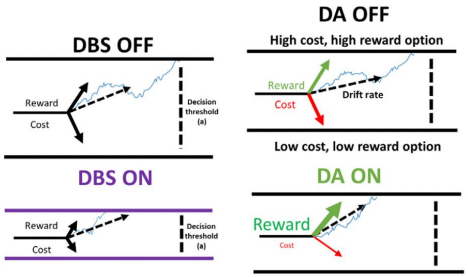
- Basic Posterior Predictive Plots
- Choice Probabilities
- Basic Psychometrics
- Quantile Probability Plots
- Model Cartoon Plots
- (> 2 choice models included)

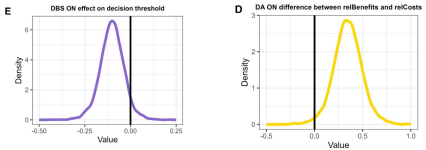
Generic plots from the wider ecosystem:

- Posterior predictives
- Model-comparison

HSSM: Supported Work



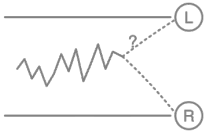


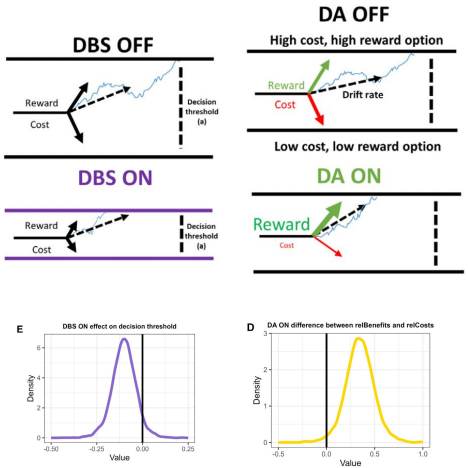


Dissociating DA and STN-DBS on cost-benefit decisions.
(Pagnier, Asaad & Frank, 2024)

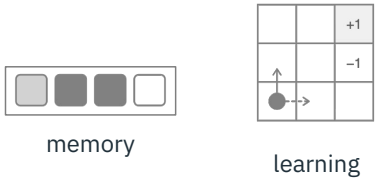
Two Parkinson's treatments with the same side effect, impulsivity, act through **two different measurable mechanisms**.

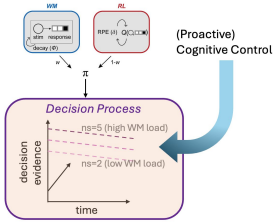
HSSM: Supported Work

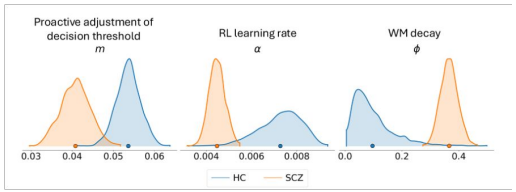




Dissociating DA and STN-DBS on cost-benefit decisions.
(Pagnier, Asaad & Frank, 2024)







Disentangling RL, WM and cognitive control mechanisms in clinical groups.
(Bera et al., 2026)

Modelling **response times as well as choices** exposes a **deficit** in schizophrenia that the **standard analysis misses**.

HSSM: Supported Work



Trusted Beyond Brown



Alexander Fengler



Krishn Bera



Andrew Zhang

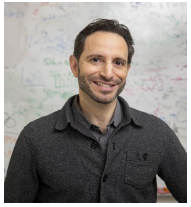


Aisulu Omar



Carlos Paniaguam





Michael J. Frank



Francesco Muia



Sicheng Liu



Aisulu Omar



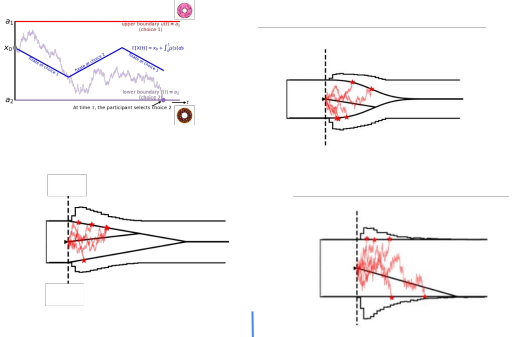
alexander_fengler@brown.edu

hssm.io

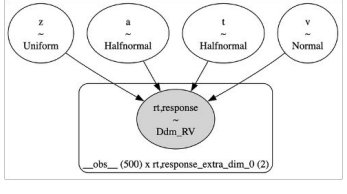
hssmentor.org

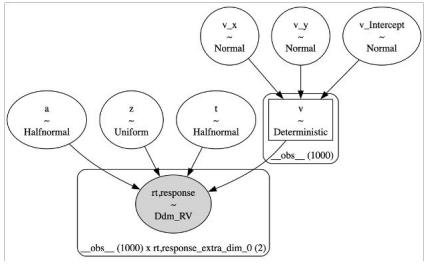
HSSM embeds in the broader SBI ecosystem

1. Choose your cognitive model



2. Build a graphical model around it

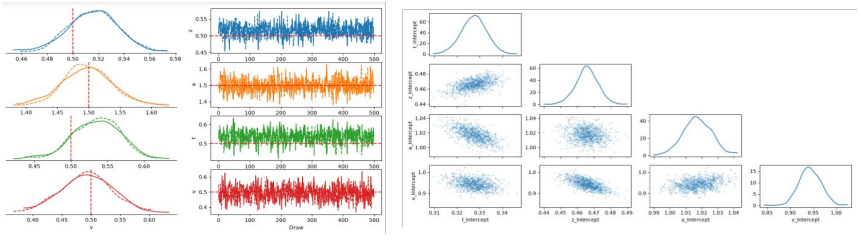




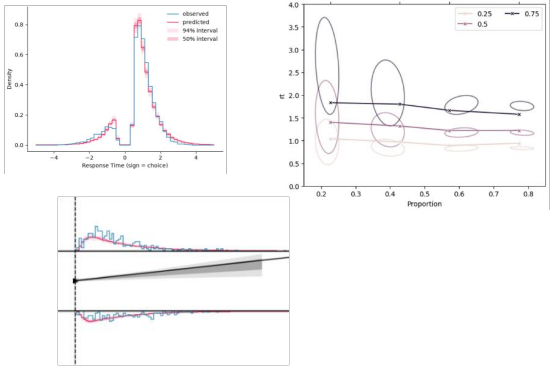
mlflow™

Track your numerical experiments.

3. Infer parameters

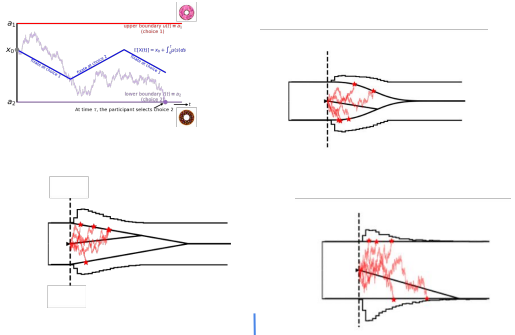


4. Analyze your fits

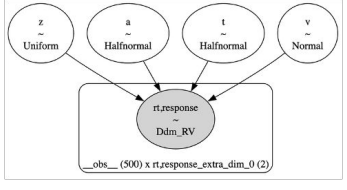


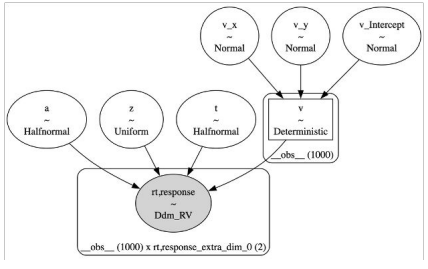
HSSM Workflow Elements

1. Choose your cognitive model

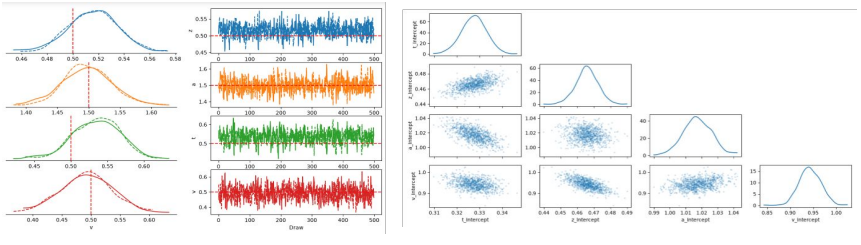


2. Build a graphical model around it

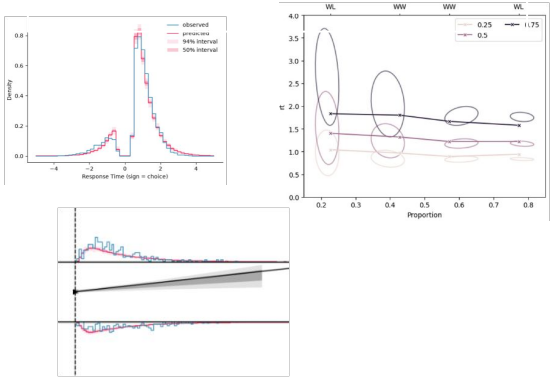




3. Infer parameters

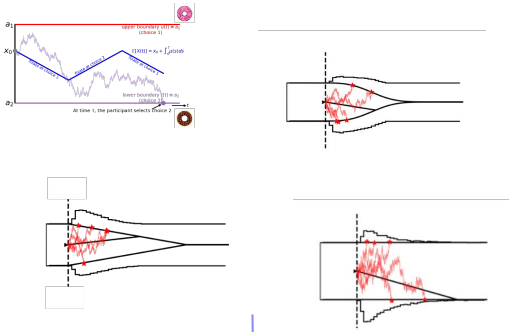


4. Analyze your fits

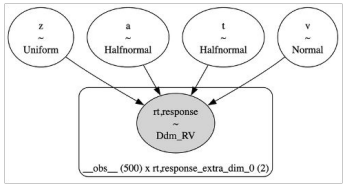


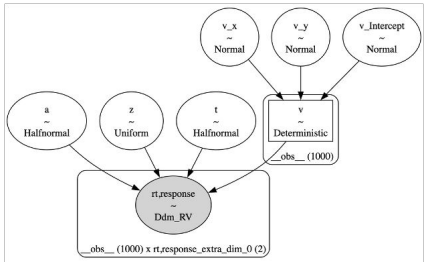
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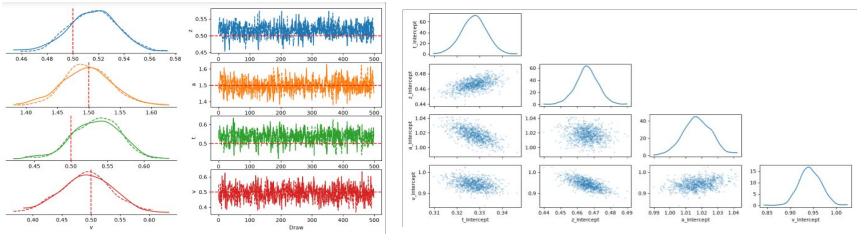


2. Build a graphical model around it

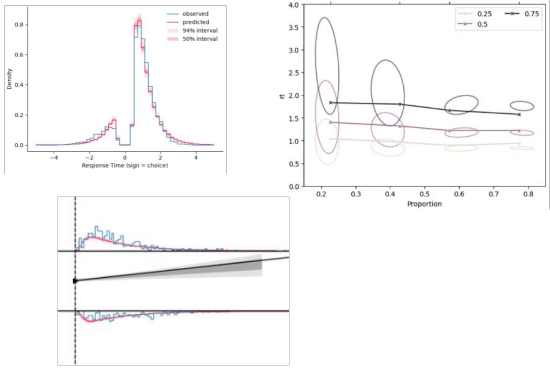




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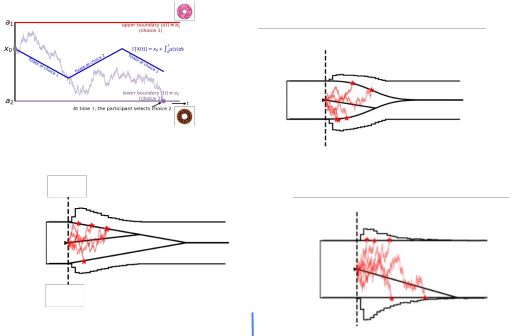


4. Analyze your fits

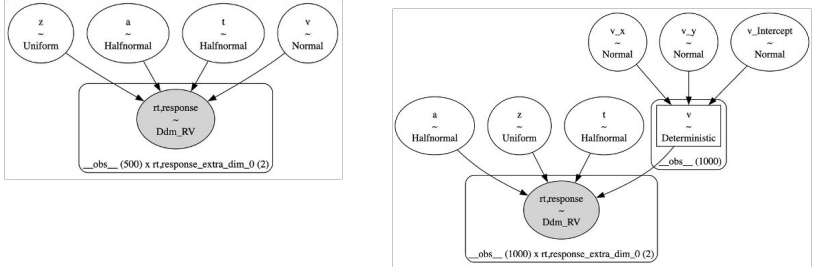


HSSM embeds in the broader SBI ecosystem

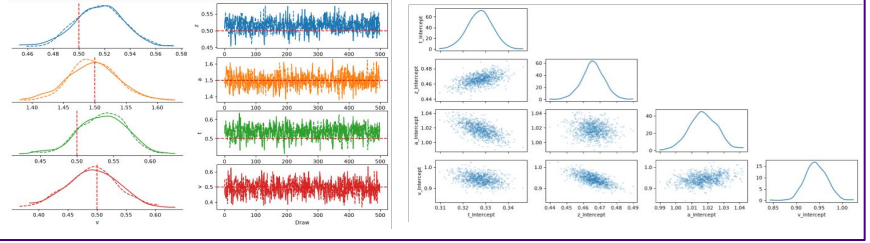
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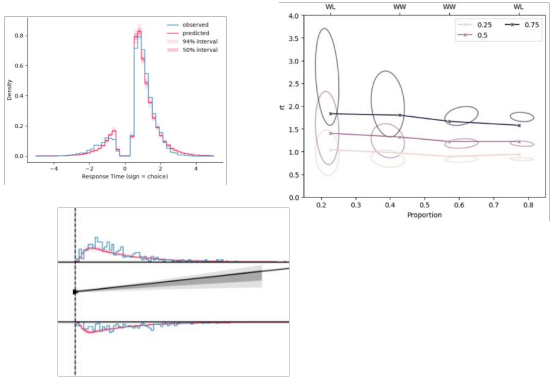
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3. Infer parameters

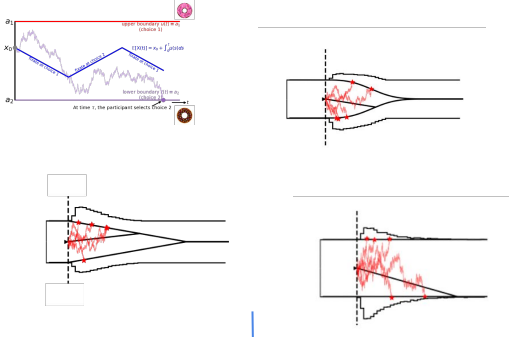


4. Analyze your fits

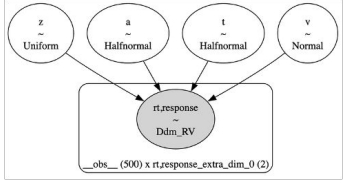


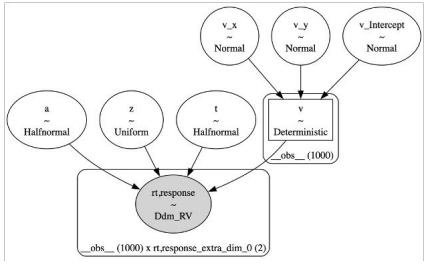
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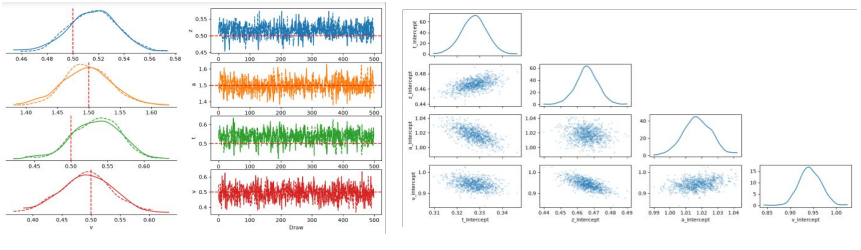


2. Build a graphical model around it





3. Infer parameters



4. Analyze your fits

