Translational Neuroscience: from dynamical systems to personalized medicine

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Eric Novik, Daniel Lee, Krzysztof Sakrejda: Generable

Outline

- Generative model of epilepsy spread
  - Seizure dynamics
  - Model validation
  - Trial logistics
- Inferential challenges
  - Bayesian workflow in context
  - What is Stan
  - Virtual Epileptic Patient (VEP) in Stan

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BRAIN
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On the nature of seizure dynamics

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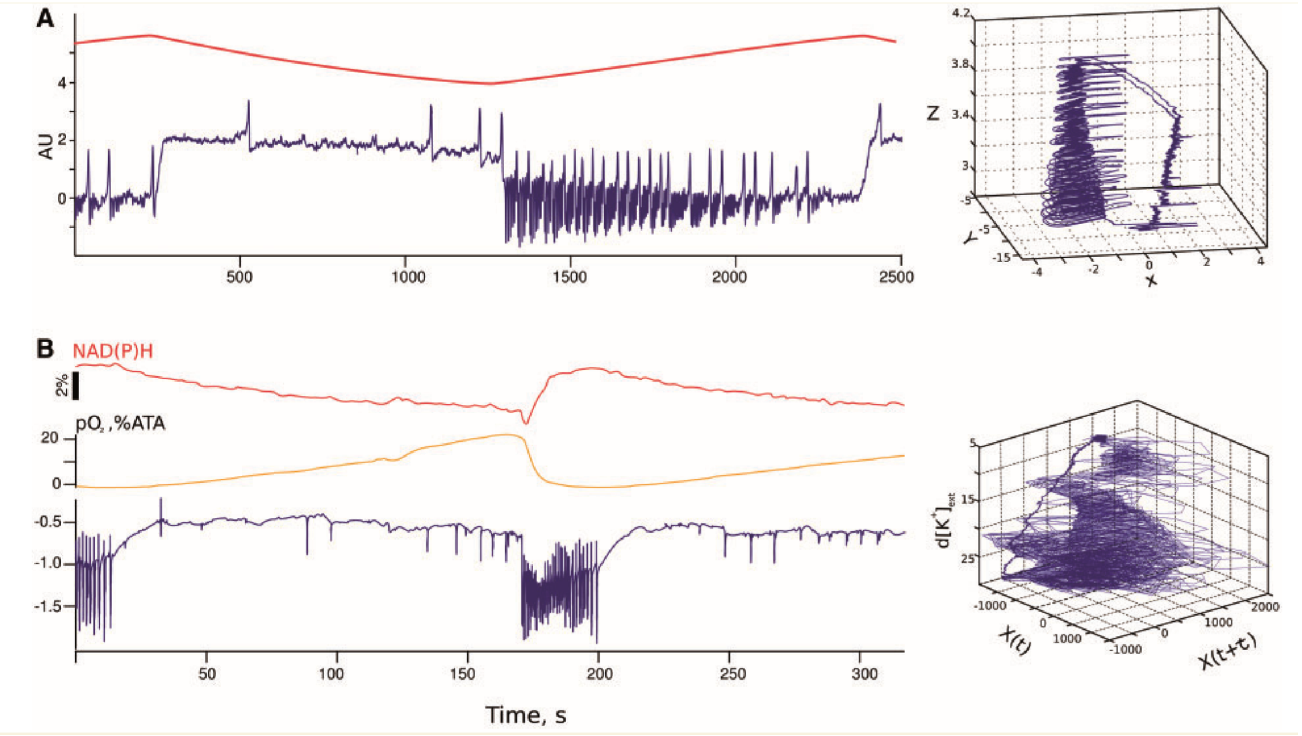
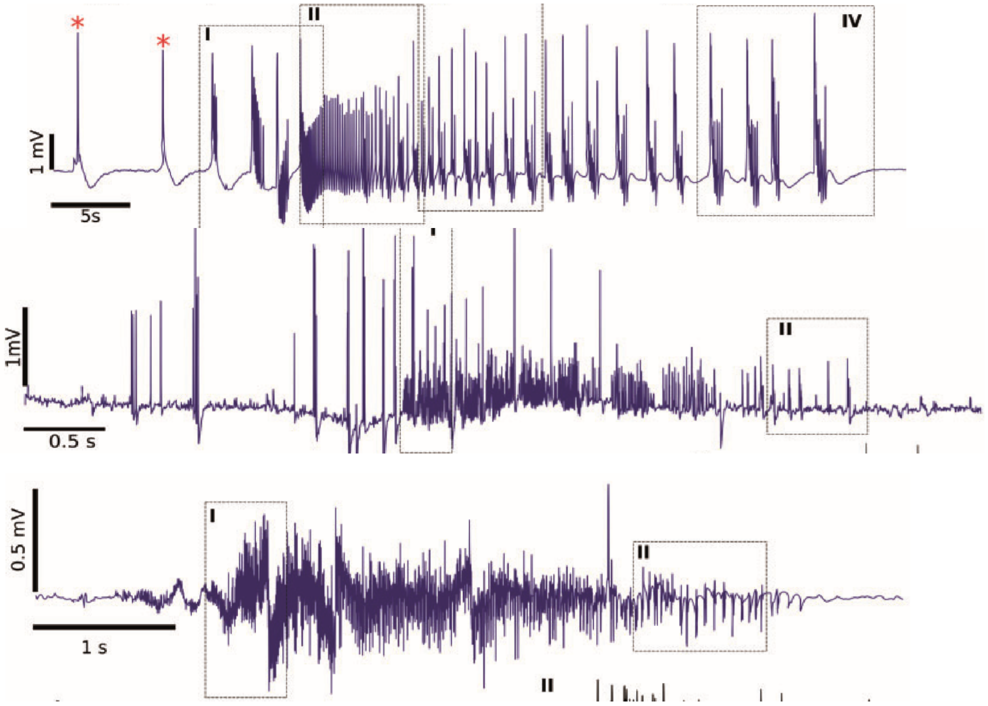


Mouse, zebrafish & human



$$
\begin{aligned}
\dot{x}_1 &= y_1 - f_1(x_1,x_2) - z + I_{rest1}\\
\dot{y}_1 &= y_0 - 5x_1^2 - y_1\\
\dot{z} &= \frac{1}{\tau_0}(4(x_1 - x_0) - z)\\
\dot{x}_2 &= -y_2 + x_2 - x_2^3 + I_{rest2} + 0.002g(x_1) - 0.3(z - 3.5)\\
\dot{y}_2 &= \frac{1}{\tau_2}(-y_2 + f_2(x_1,x_2))
\end{aligned}
$$

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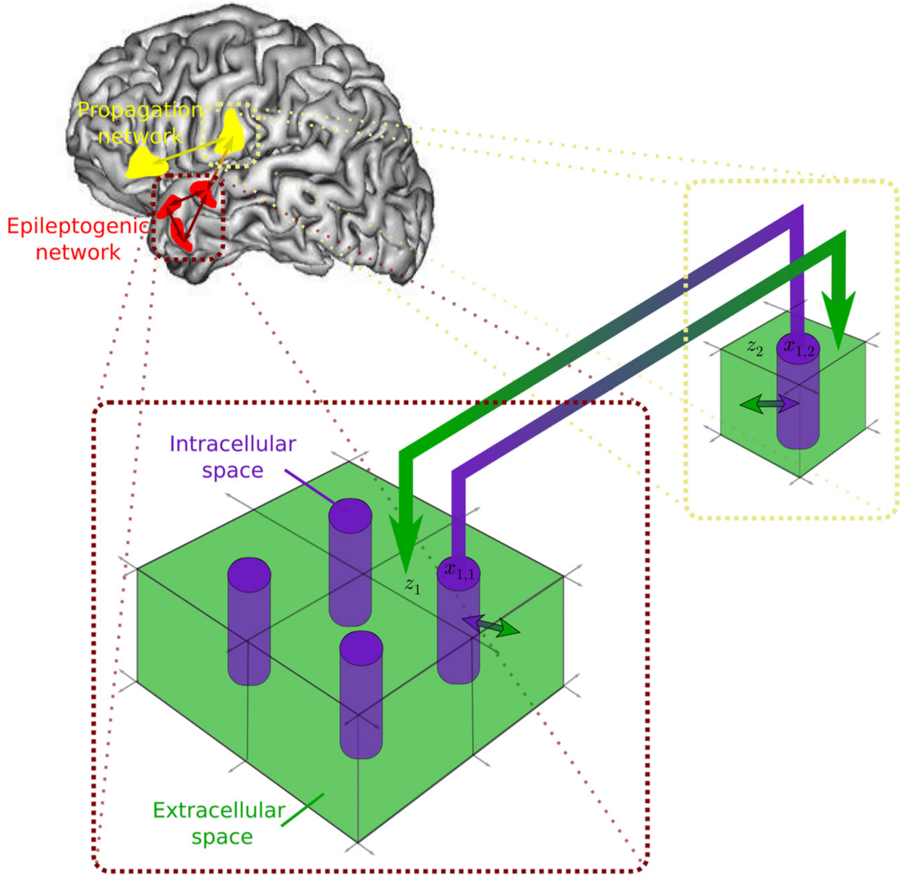
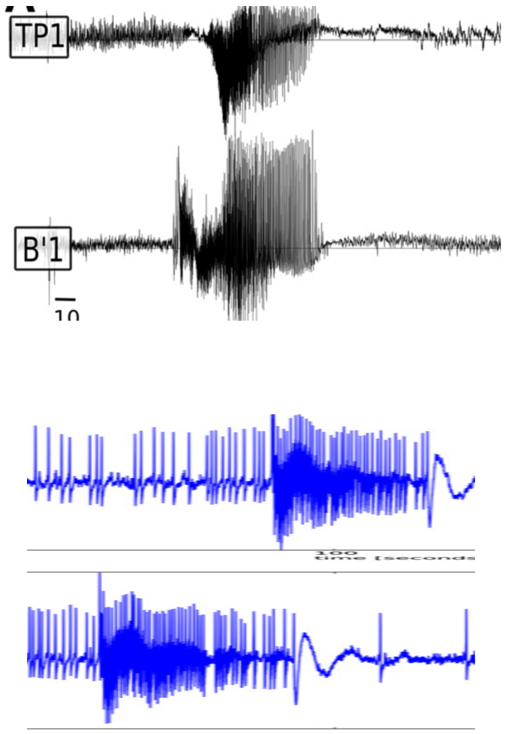
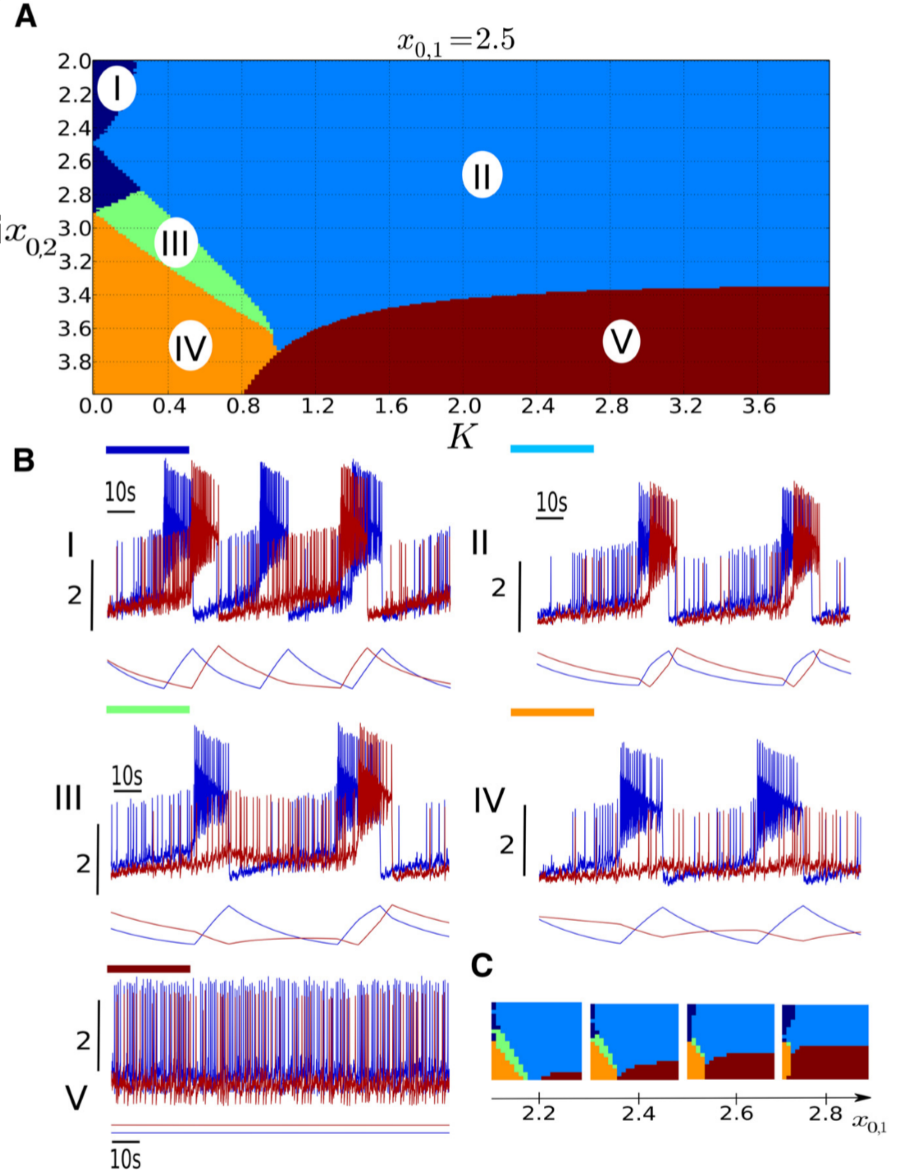
Permittivity Coupling across Brain Regions Determines Seizure Recruitment in Partial Epilepsy

Timothée Proix,[1,2] Fabrice Bartolomei,[1,2,3] Patrick Chauvel,[1,2,3] Christophe Bernard,[1,2] and Vi



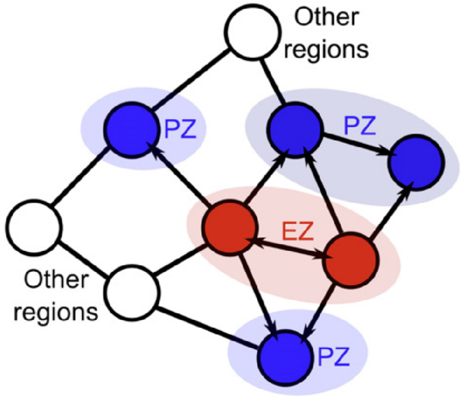


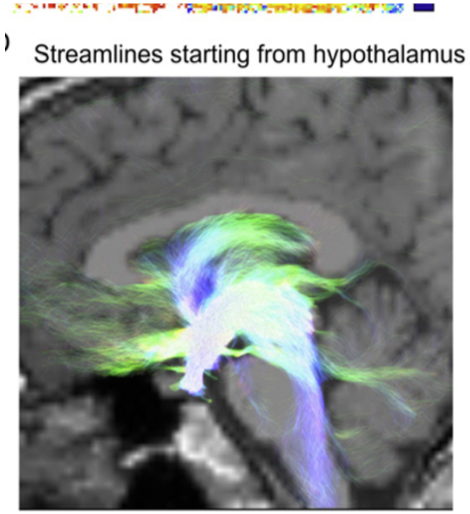


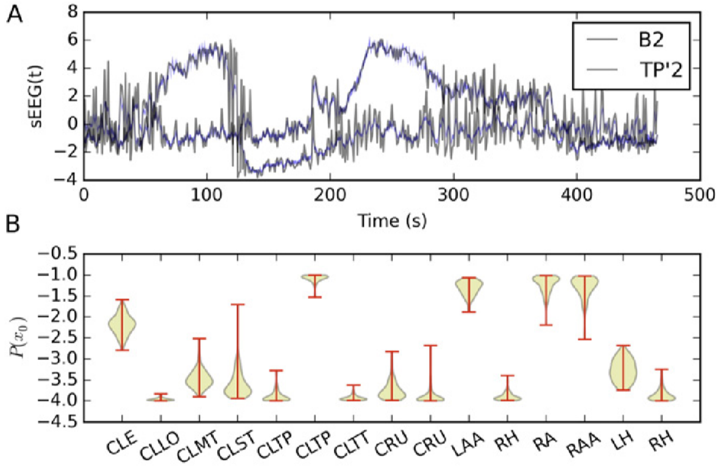
The Virtual Epileptic Patient: Individualized whole-brain models of epilepsy spread

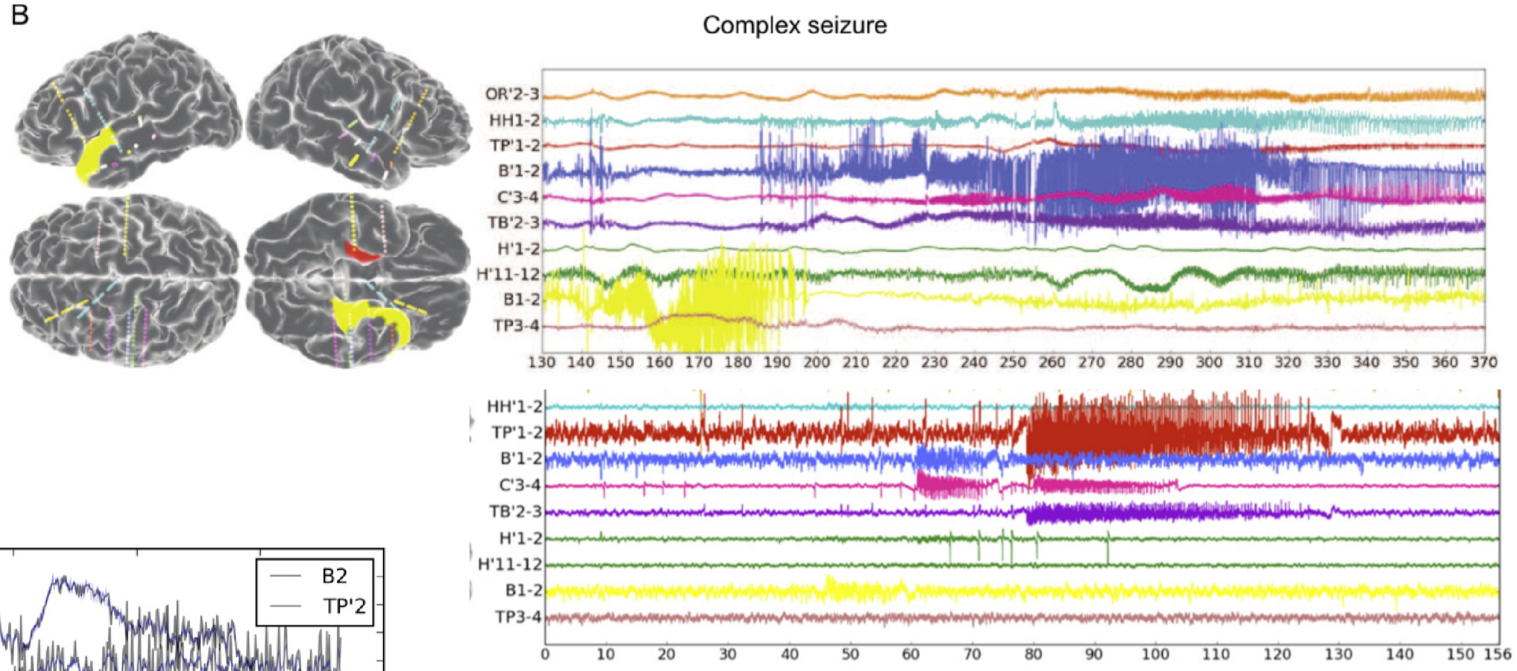
NeuroImage 145 (2017) 377–388

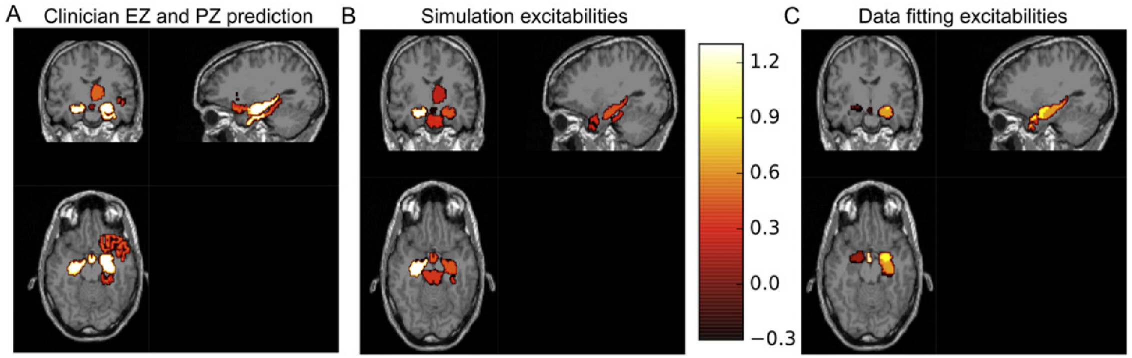
V.K. Jirsa [a,*], T. Proix [a], D. Perdikis [a], M.M. Woodman [a], H. Wang [a], J. Gonzalez-Martinez [d], C. Bernard [a], C. Bénar [a], M. Guye [c], P. Chauvel [a,d], F. Bartolomei [a,b]



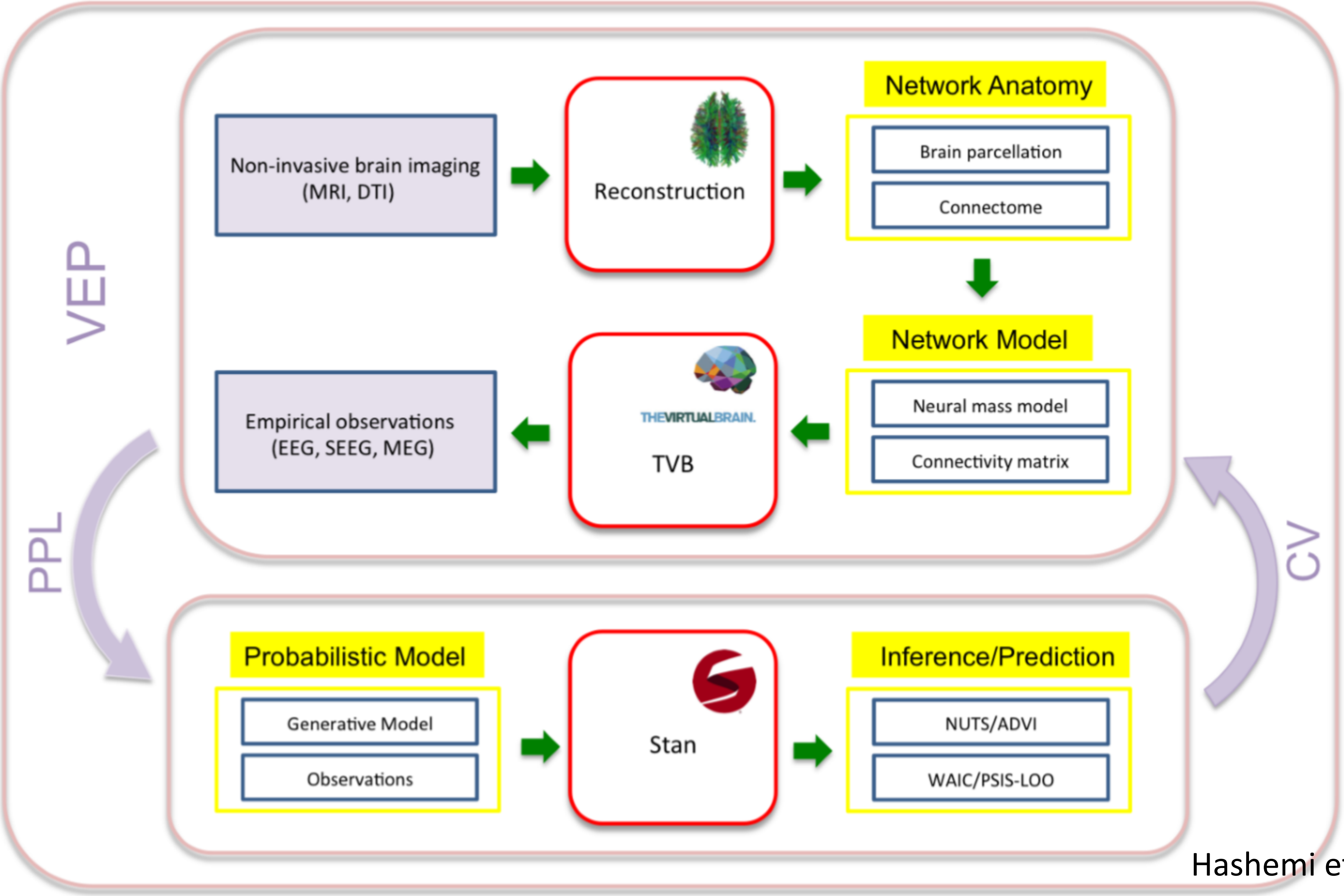






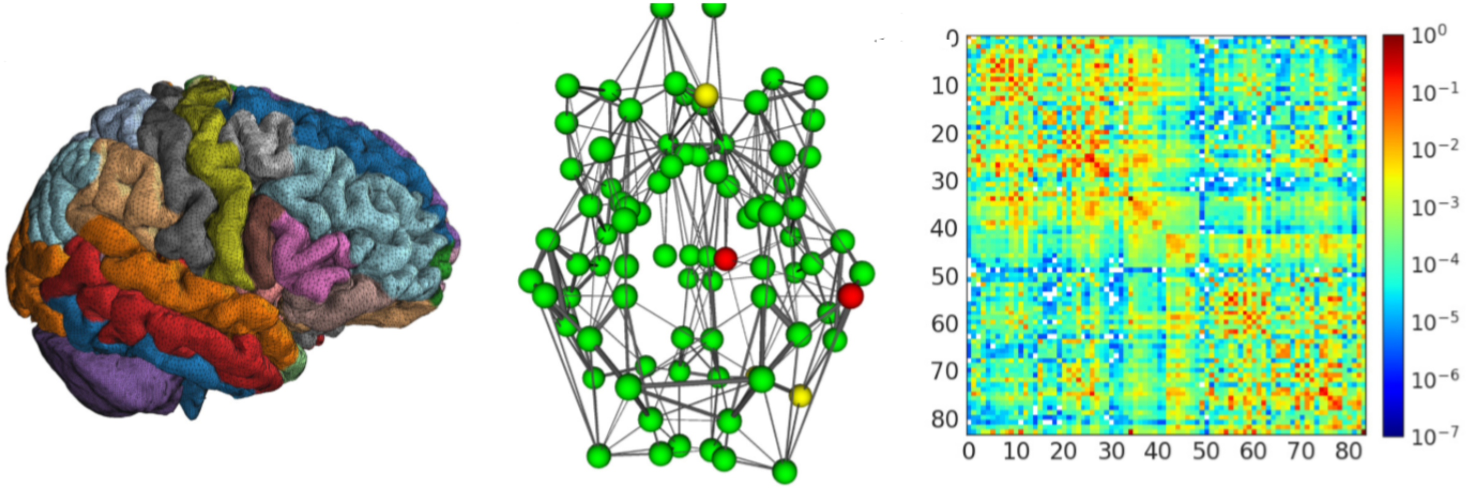


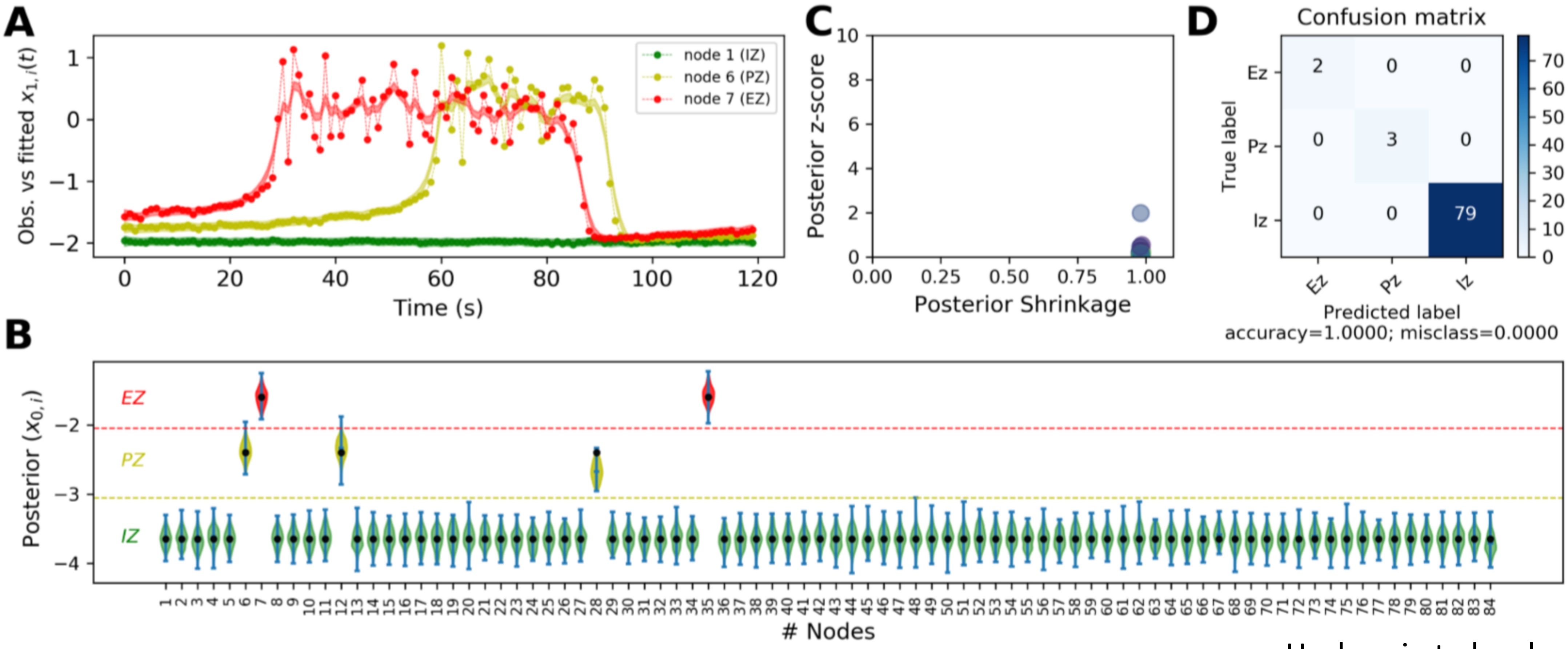
Model validation scheme



Hashemi et al, submitted

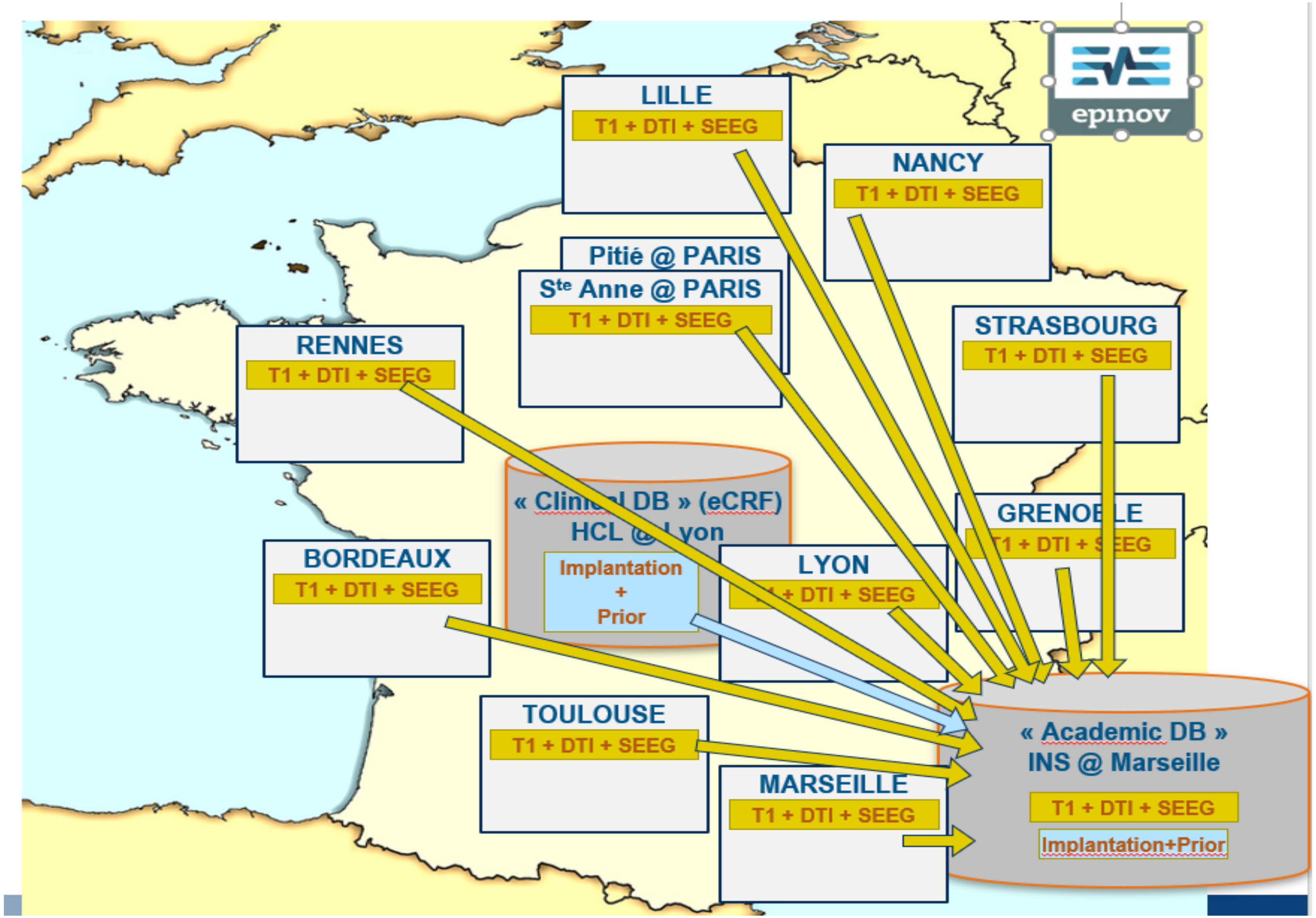
Model validation





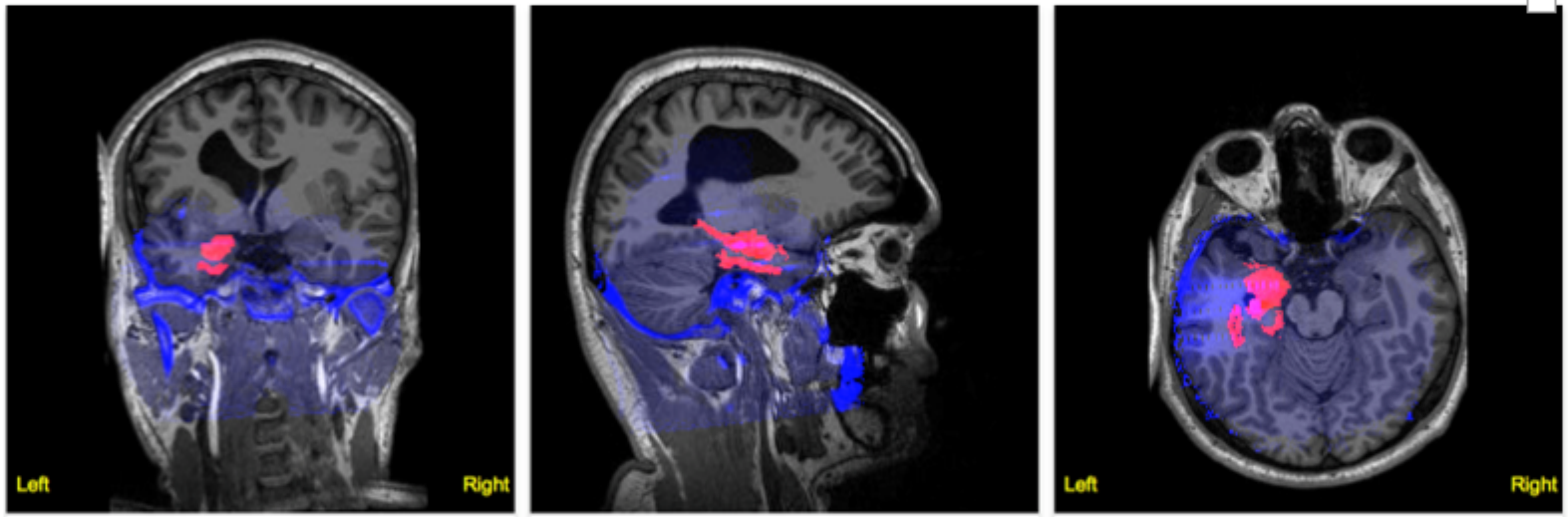
Hashemi et al, submitted

National data collection during trial

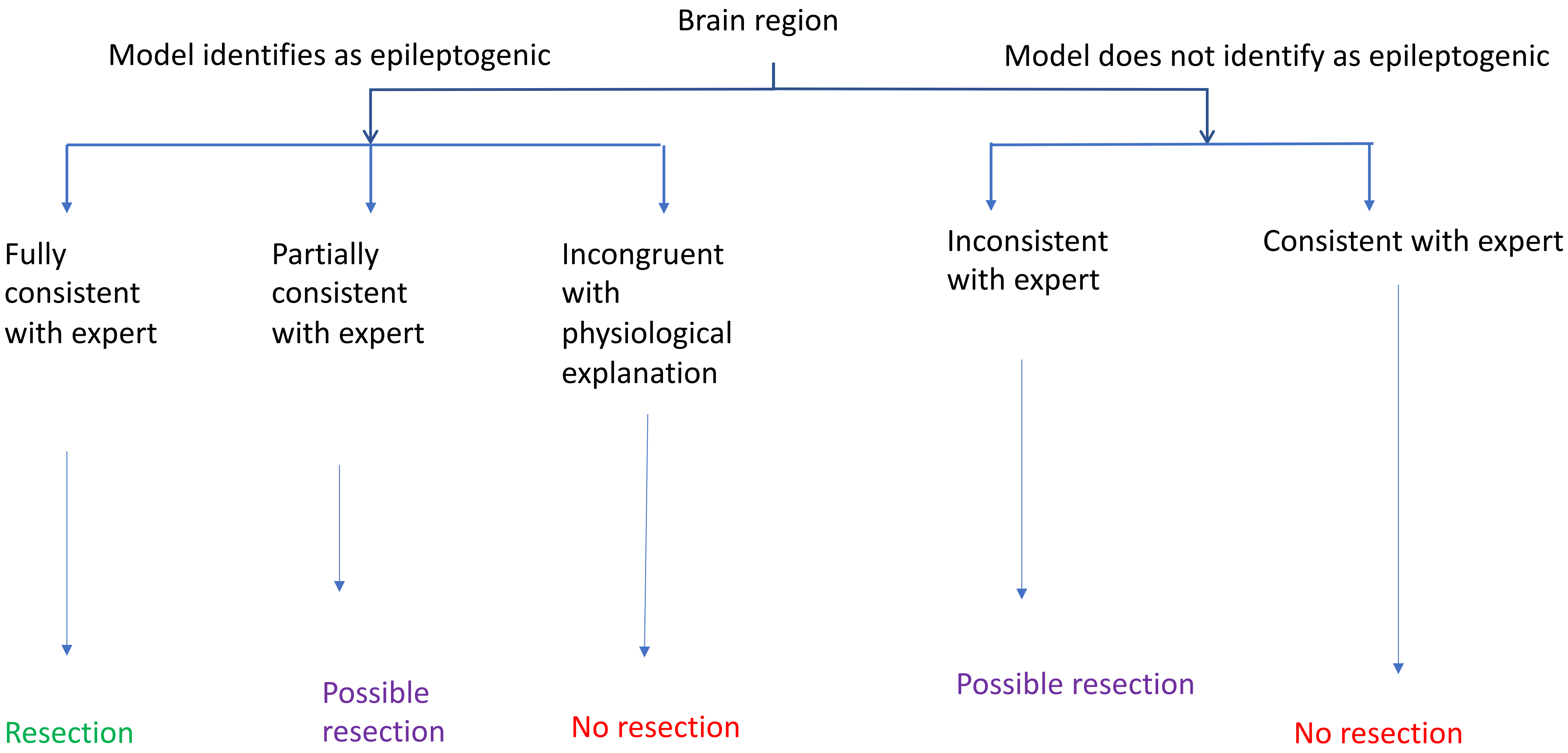


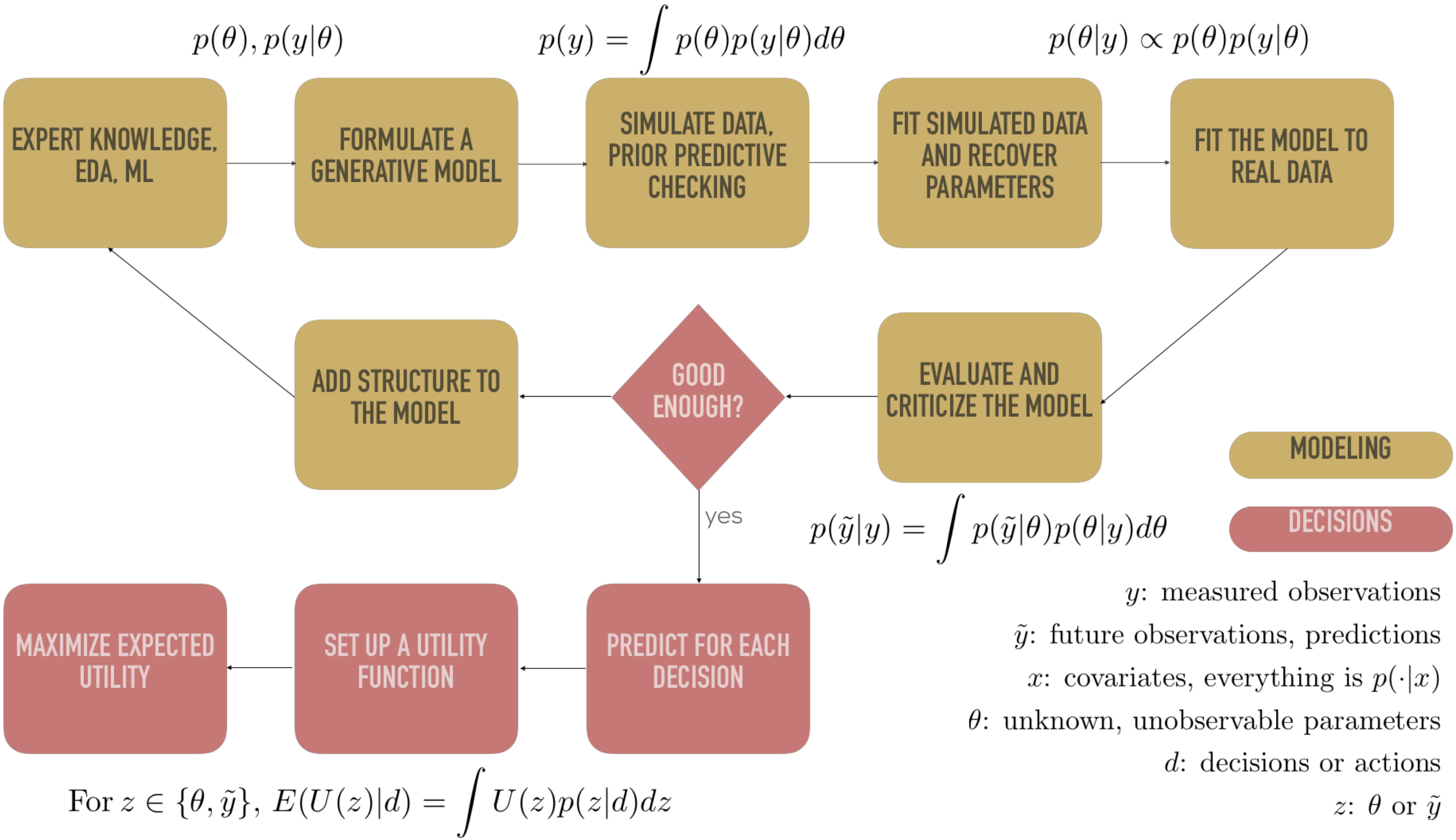
Clinical report example

ROI	EZ	Confidence	Distribution
Left-Hippocampus	Yes	100%	
Left-Parahippocampal gyrus, parahippocampal part of the medial occipito-temporal gyrus, (T5)	Yes	99%	
Left-Amygdala	Yes	99%	
Left-Anterior transverse collateral sulcus	Yes	98%	
Left-Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus	No	31%	
Left-Temporal pole	No	27%	



Surgical decision tree





$p(\theta), p(y|\theta)$
$p(y) = \int p(\theta)p(y|\theta)d\theta$
$p(\theta|y) \propto p(\theta)p(y|\theta)$
EXPERT KNOWLEDGE, EDA, ML
FORMULATE A GENERATIVE MODEL
SIMULATE DATA, PRIOR PREDICTIVE CHECKING
FIT SIMULATED DATA AND RECOVER PARAMETERS
FIT THE MODEL TO REAL DATA
ADD STRUCTURE TO THE MODEL
GOOD ENOUGH?
EVALUATE AND CRITICIZE THE MODEL
MODELING
DECISIONS
yes
$p(\tilde{y}|y) = \int p(\tilde{y}|\theta)p(\theta|y)d\theta$
MAXIMIZE EXPECTED UTILITY
SET UP A UTILITY FUNCTION
PREDICT FOR EACH DECISION
y: measured observations
$\tilde{y}$: future observations, predictions
x: covariates, everything is $p(\cdot|x)$
θ: unknown, unobservable parameters
d: decisions or actions
z: θ or $\tilde{y}$
For $z \in \{\theta, \tilde{y}\}$, $E(U(z)|d) = \int U(z)p(z|d)dz$

- High level statistical modeling language
  - Defines joint log density
  - Statically typed
  - Turing complete

$$p(\theta, x)$$

- Inference algorithms
  - Full Bayes (MCMC): No-U-Turn Sampler

$$\{\theta^{(1)}, \theta^{(2)}, \ldots, \theta^{(N)}\} \sim p(\theta \mid x)$$

  - Approximate Bayes: ADVI

$$\hat{p}(\theta \mid x) \approx q(\hat{\phi})$$

$$\hat{\phi} = \underset{\phi}{\operatorname{argmin}}\ D_{\mathrm{KL}}\left(q(\theta \mid \phi) \,||\, p(\theta \mid x)\right)$$

  - Optimization: L-BFGS

$$\hat{\theta} = \underset{\theta}{\operatorname{argmax}}\ p(\theta, x)$$

- Interfaces
  - R, Python, cli, Julia, Matlab, Stata

Stan

$$
\begin{aligned}
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\end{aligned}
$$

```
functions {
    row_vector z_step(row_vector x, row_vector z, row_vector x0, matrix FC, vector Ic,
        real time_scale, row_vector z_eta, real sigma, real tau0) {
        int nn = num_elements(z);
        row_vector[nn] z_next;
        matrix[nn, nn] D = vector_differencing(x);
        row_vector[nn] gx = to_row_vector(rows_dot_product(FC, D) - Ic .* to_vector(1.8 + x));
        row_vector[nn] dz = inv(tau0) * (4 * (x - x0) - z - tanh(gx));
        z_next = z + (time_scale * dz) + z_eta * sigma;
        return z_next;
    }
}
```

Statistical challenges

- Computation time, convergence, and posterior geometry are linked
- As specified, multi-modality in the parameter space
    - Easier problem for optimization or ADVI when solution is not guaranteed to be optimal
    - Mix of parameter constraints and priors to limit the parameter space to limit the solution
    - Sparse data exacerbates the problem: if there was more data, we could identify the parameters.
- Revised the model many times (over 10 iterations)

Merci beaucoup!

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