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Bayesian Markov Renewal Mixed Models for Vocalization Syntax

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FOXP2-related speech and language disorder

Description



FOXP2-related speech and language disorder is a condition that affects the development of speech and language starting in early childhood. Affected individuals have a speech problem known as apraxia, which makes it difficult to produce sequences of sounds, syllables, and words. This condition results from abnormalities involving parts of the brain  that plan and coordinate movements of the lips, mouth, and tongue. Children with apraxia typically say their first words later than other children. Their speech is often difficult to understand, although the clarity of speech improves somewhat over time. Some affected individuals also cannot cough, sneeze, or clear their throats.

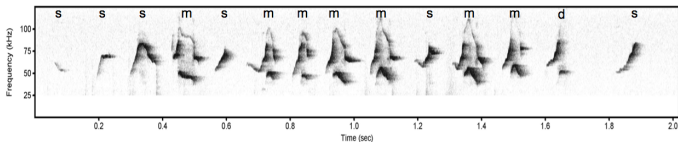
In addition to having problems with producing speech (expressive language), people with *FOXP2*-related speech and language disorder may have difficulty with understanding speech (receptive language). Some also have trouble with other language-related skills, such as reading, writing, spelling, and grammar. In some affected individuals, problems with speech and language are the only features of the condition. Others also have delayed development in other areas, including motor skills such as walking and tying shoelaces, and autism spectrum disorders, which are conditions characterized by impaired communication and social interaction.

¹ <https://medlineplus.gov/genetics/condition/foxp2-related-speech-and-language-disorder/>

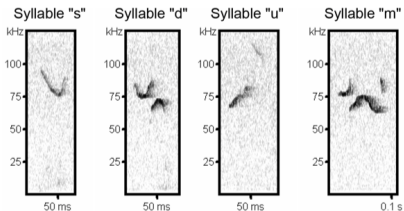


Mouse Vocalization Experiments

- ▶ FoxP2 gene is found in similar form in mice
- ▶ Adult mice 'sing' ultrasonic sounds to communicate



- ▶ 4 types of syllables: $\{d, s, m, u\}$





FoxP2 Data Set

- ▶ 18 mice, 49 songs, 70818 rows
- ▶ Covariate 1: genotype
 - **F**oxP2: 10 with the FoxP2 mutation
 - **W**ildtype: 8 without the FoxP2 mutation
- ▶ Covariate 2: social context
 - **U**: fresh female mouse urine placed in the cage
 - **L**: awake female mouse placed in the cage
 - **A**: anesthetized female mouse placed on the cage

ID	Genotype	Context	Syllable	Inter-Syllable Intervals (ISI)
1	<i>F</i>	<i>A</i>	<i>s</i>	0.082
1	<i>F</i>	<i>A</i>	<i>s</i>	0.017
⋮	⋮	⋮	⋮	⋮
18	<i>W</i>	<i>L</i>	<i>s</i>	1.546
18	<i>W</i>	<i>L</i>	<i>d</i>	0.712



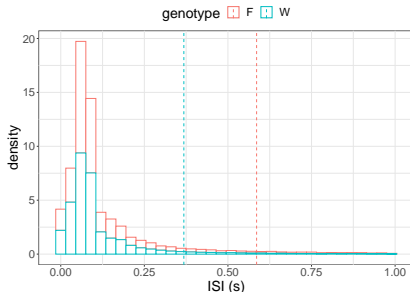
Analyzing the FoxP2 Data Set

- ▶ Goal: investigate the influence of the FoxP2 mutation & social context by analyzing syllable transition dynamics
- ▶ Past analyses

Holy and Guo (2005)	first Markov model on syllable transitions
Chabout et al. (2015, 2016)	statistical tests for local and global syntax difference across genotypes and contexts
Sarkar et al. (2018)	models inter-syllable intervals (ISI) as an artificial syllable (x) and built a model for 5 states $\{d, m, s, u, x\}$

Properly Modeling ISI is Necessary

- ▶ ISI is an indicator of vocal impairment
 - Longer ISIs \implies difficulties in pronouncing syllables
- ▶ ISI as an artificial syllable (x) results in loss of information
 - Syllable transitions will be dominated by $x \rightarrow x$
 - Interferes with the inference of regular syllables

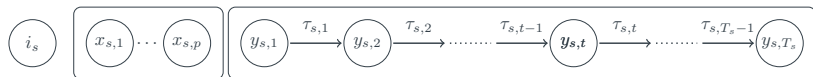




Bayesian Markov Renewal Mixed Model (BMRMM)

State transitions and ISIs are modeled separately.

1. State transitions with state space $\{d, m, s, u\}$
 - Dirichlet distributions
2. Inter-syllable interval lengths
 - Mixture gamma distributions with K components





Mixed Effects Mixture Probabilities for ISI

ISI follows a mixture gamma distribution with K components.

- ▶ Mouse i with genotype \mathbf{x}_1 , context \mathbf{x}_2 , prev. syllable \mathbf{y}_{t-1}
- ▶ The probability of being in the k -th component is

$$P_{isi, \mathbf{x}_1, \mathbf{x}_2, \mathbf{y}_{t-1}}^{(i)}(k) = \pi_{isi,0}^{(i)}(k) \cdot \lambda_{isi, \mathbf{x}_1, \mathbf{x}_2, \mathbf{y}_{t-1}}(k) \\ + \pi_{isi,1}^{(i)}(k) \cdot \lambda_{isi}^{(i)}(k).$$

- ▶ **Population-level effect** is determined by \mathbf{x}_1 , \mathbf{x}_2 and \mathbf{y}_{t-1}
- ▶ **Individual-level effect** is determined by i
- ▶ $\pi_{isi,0}^{(i)}(k) + \pi_{isi,1}^{(i)}(k) = 1$



Cluster Inducing Mechanism for Covariates

- ▶ Different levels of a covariate may have similar effects
- ▶ Levels with same effect should be clustered together
 - Help identify the significant covariates
 - Null hypothesis: 1 cluster for all levels of a covariate
- ▶ The mixture probability now depends on clustering, instead of covariate levels:

$$P_{isi, x_1, x_2, y_{t-1}}^{(i)}(k) \Rightarrow P_{isi, g_1, g_2, g_3}^{(i)}(k),$$

where g_1, g_2, g_3 are cluster indices.



Inferences for Transition Probabilities

- ▶ Mouse i with genotype x_1 under context x_2
- ▶ The transition probability from syllable y_{t-1} to y_t is

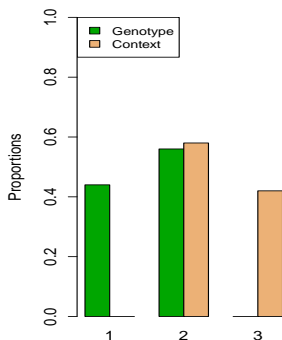
$$P_{trans,x_1,x_2}^{(i)}(y_t | y_{t-1})$$

- ▶ Similarly, the transition probability is a convex combination of the population- and individual-level effect
- ▶ Similar covariate levels are again clustered

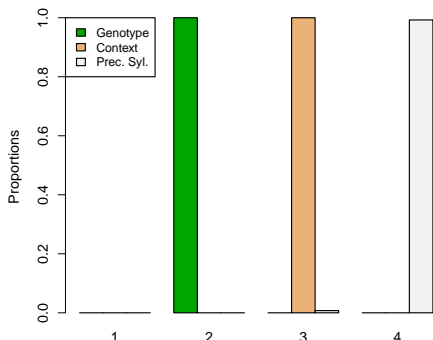
$$\begin{aligned} P_{trans,x_1,x_2}^{(i)}(y_t | y_{t-1}) &\implies \\ P_{trans,h_1,h_2}^{(i)}(y_t | y_{t-1}) &= \pi_{trans,0}^{(i)}(y_{t-1}) \cdot \lambda_{trans,h_1,h_2}(y_t | y_{t-1}) \\ &\quad + \pi_{trans,1}^{(i)}(y_{t-1}) \cdot \lambda_{trans}^{(i)}(y_t | y_{t-1}) \end{aligned}$$

Results – Global Tests

- ▶ All covariates are significant for ISIs
- ▶ The effect of the FoxP2 mutation on transition probabilities is weaker, in contrast to previous analyses



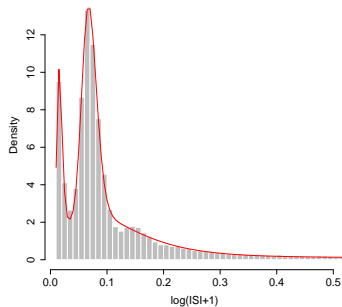
(a) Transition probabilities



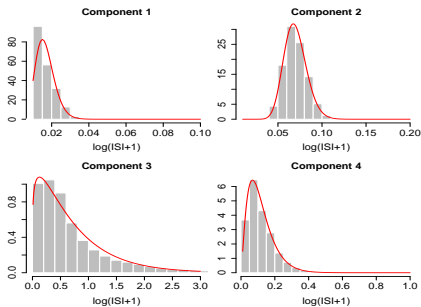
(b) Inter-syllable intervals

Results – Fitting of ISI

- ▶ The estimated posterior distribution fits ISI well
- ▶ Component 3 represents larger values of ISI



(c) Histogram of ISI with estimated posterior mean



(d) Histogram by mixture component from last MCMC iteration



Results – Mixture Probabilities by Covariate

- ▶ Recall: Component 3 represents larger values of ISI
- ▶ Mice with the mutation (F) have a significant higher mixture probability in Component 3
- ▶ Mice under context L seem to have shorter ISI

Component 1	0.09	0.11	0.06	0.17	0.06
Component 2	0.4	0.42	0.44	0.3	0.48
Component 3	0.21	0.11	0.2	0.12	0.17
Component 4	0.3	0.36	0.29	0.41	0.29
	F	W	U	L	A



Conclusions

Bayesian Markov Renewal Mixed Model (BMRMM)

- ▶ BMRMM is suitable to analyze categorical data sequences associated with different individuals
- ▶ Both trans. prob. and continuous ISI are modeled properly
- ▶ Transition/Mixture probabilities are convex combinations of the population- and individual-level effects
- ▶ Covariate levels with similar effect are clustered together

Preprint available at <https://arxiv.org/abs/2107.07648>

R package **BMRMM** is published on CRAN

<https://cran.r-project.org/web/packages/BMRMM/index.html>