The Effects of Enzyme Reaction Rates With Puromycin

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1 Introduction

Puromycin is an antibiotic protein synthesis inhibitor which can affect the speed of enzymatic processes. In order to study its effects, biologist Margaret Treloar performed a controlled experiment by introducing Puromycin to a set of Galactosyltransferase processes within golgi membranes. She measured the reaction rate of the process with a given concentration of enzyme and repeated the process for reactions treated with Puromycin.Using Bayesian analysis, we will explore Puromycin catalytic effects on enzymes.

2 The Data

The data from the experiment consists of a concentration and reaction rate metric as well as an indicator for experiments that are treated with Puromycin.

Below is a density plot of our concentration variable and the log transform of the variable:

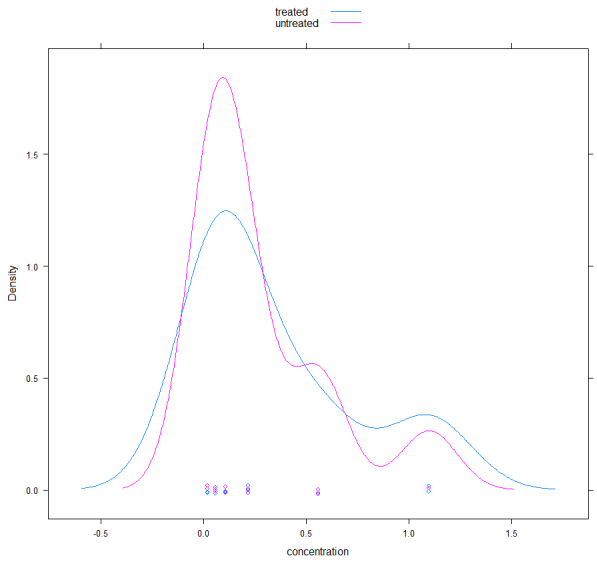

Figure 1: Density plot of concentration

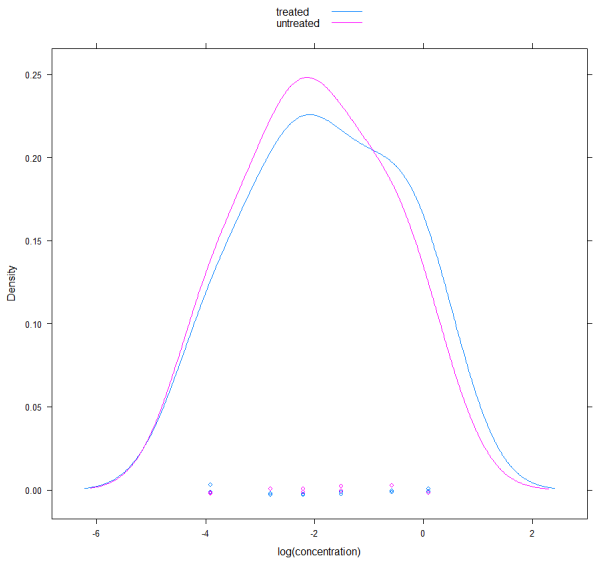

Figure 2: Density plot of log concentration

The original distribution of the variable does not appear normal and has a right skew, indicating we may want to transform it. After the log transform, the distribution for the variable looks normally distributed. From these results, we will transform the variable for our model.

Below is a density plot of our rate variable:

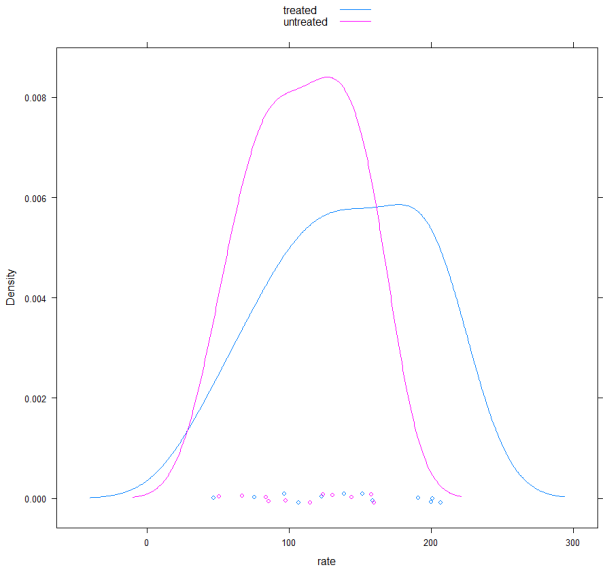

Figure 3: Density plot of rate

Our data looks normally distributed for both groups. However, we can notice that the treated group has more variance then compared to our untreated group.

Lastly, we can see if Puromycin had an effect by putting a best fit line over our two metric variables. We can fit a line over all the data and a line over the individual groups and look at the total variance:

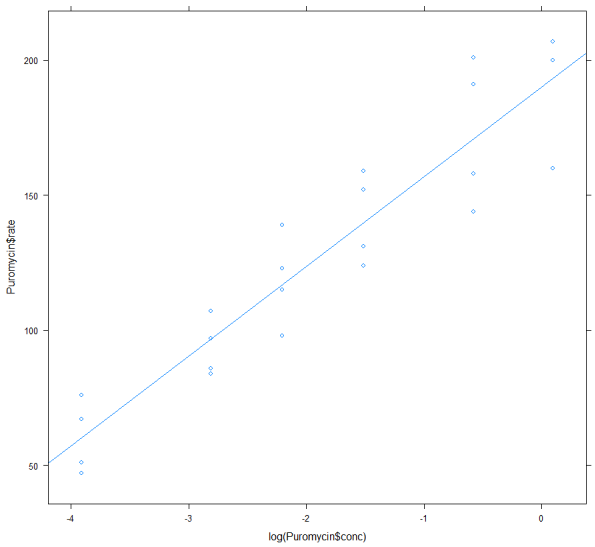

Figure 4: Simple linear model

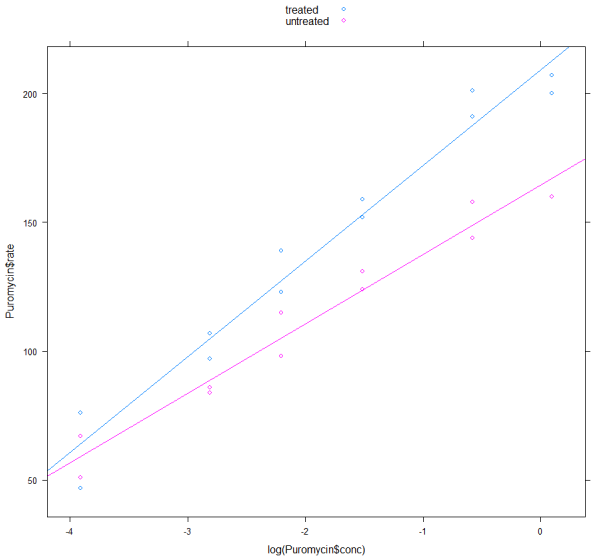

Figure 5: Simple linear model with groups

It is clear that the addition of Puromycin changed the reaction rate as the lines around the individual groups are tighter than that of the model over the whole data. Therefore, we will build a model that can estimate the individual slopes and y-intercepts of both groups.

3 The Model

Our model is concerned with building a linear model over both treated and untreated groups using concentration to predict reaction rate. Our linear model is defined as $\sum_{j \in \{T,U\}} a_{[j]} + a\_met_{c,[j]} * \log(c_{[j],i})$ where j is an indicator for treated and untreated cases, c is a given concentration, a is the y-intercept, a_met is the slope and is multiplied by concentration. We built a model that finds the posterior distribution of the slope and y-intercept parameters. To make our model more robust, we utilized a t-distribution to model the posterior. Below is a model diagram depicting how each parameter is defined:

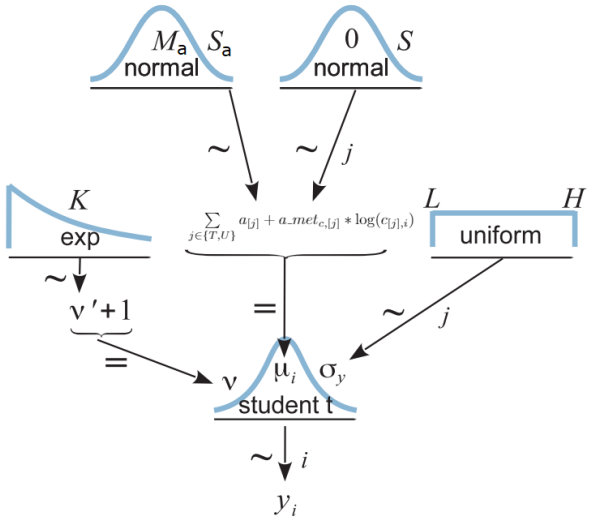

Figure 6: Simple linear model

3.1 Prior distribution parameters

We set unique priors for our y-intercept and slope on both groups. The y-intercept and slope come from a normally distributed hyper-prior centered at 0 but with an informed standard deviation from the data. We then estimate our μ parameter from the definition of our linear model for our t-distribution. Our other t-distribution parameters are shared with both groups and are sampled from their respective distributions in the diagram with vague priors. Below is the code defining these parameters.

```
# Priors of model:
ySigma ~ dunif( residSD/100 , ySD*10 )
nu ~ dexp(1/30.0)
for ( j in 1:NxNomLvl ) { a[j] ~ dnorm( 0.0 , 1/aSigma^2 )
                          aMet[j] ~ dnorm( 0 , 1/(2*ySD/xMetSD)^2 ) }
aSigma ~ dgamma( agammaShRa[1] , agammaShRa[2] )
```

4 The Posterior

4.1 MCMC Diagnostics

We can ensure the accuracy of our posterior distribution due to our MCMC diagnostics. Each of our chains' metrics satisfy the assumptions which provide evidence showing that the chains converged correctly. The chains' all showed random behavior during the run period. All of our chains' auto-correlation and shrink factors converge towards 1 and 0 respectively and our density plots show tightly clustered distributions. If you would like see the diagnostic maps, please refer to the code.

4.2 Establishing ROPE parameters

Since we are looking to see if Puromycin has an effect on the enzyme's reaction rate, we can conduct a null hypothesis test by defining ROPE parameters when comparing the difference of the model's slopes. Our null hypothesis would state that Puromycin has no effect on the reaction rate, thus the difference would be zero. We can set a ROPE value at 0 and give it a range of 0.5 on the edges. If our HDI falls within this range, we will not reject the null hypothesis.

4.3 Simulation results

Below are the accompanying estimated parameters and graphs generated by our MCMC simulation:

	Mean	Median	Mode	ESS	HDImass	HDIlow	HDIhigh
a[1] treated	208.770705	208.74100	209.587855	9561.0	0.95	199.21900	218.7610
a[2] untreated	164.308363	164.26100	164.099853	8697.7	0.95	153.17000	175.4290
aMet[1] treated	84.859698	84.76730	84.377844	9684.7	0.95	75.09510	95.7445
aMet[2] untreated	61.927519	61.93460	62.032796	8332.0	0.95	50.51570	71.9876
aSigma	188.508042	171.77400	139.633807	11001.0	0.95	74.16180	339.1330
ySigma	9.527787	9.28455	8.761625	10661.4	0.95	6.35466	13.1760
nu	36.444412	27.57270	12.618748	11001.0	0.95	1.28268	98.1994
treated.v.untreated	22.932180	22.82080	21.714744	8690.4	0.95	8.23190	38.3493

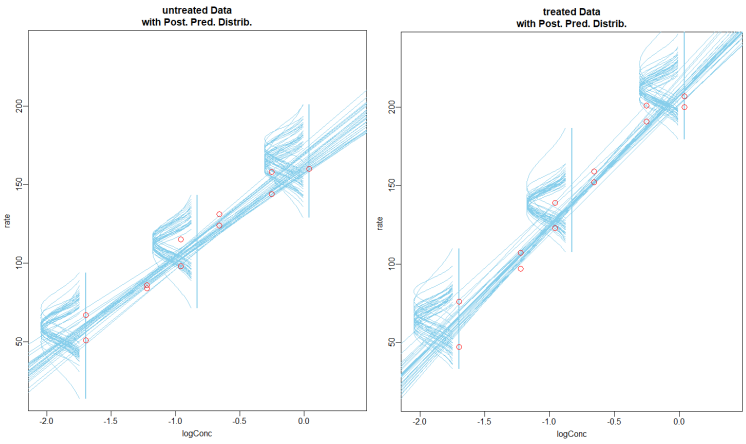

Figure 7: Linear Reg w/ t-noise distributions

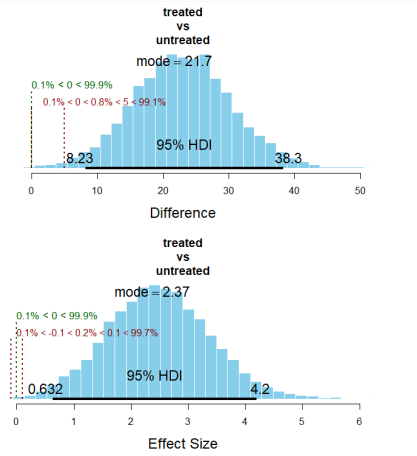

Figure 8: Posterior difference in slopes

Our ν parameter is small and $sigma_y$ parameter is large indicating that there is very little variance within our predictive model. The data is closely represented by our linear models. For our treated group, our estimated credible ranges for our y-intercept (or x-intercept in these graphs) are 199-218 and its slope is in the HDI range of 75-95. On the other hand, the untreated group has a y-intercept in the HDI range of 153-175 and credible values for the slope in the range of 50-71. We can see that the treated group clearly has a faster reaction rate than untreated reactions. We can further see this in the slope parameter comparison in figure 7. Our HDI of the differences does not include ROPE range, indicating that we reject the null hypothesis. We have sufficient evidence to state that Puromycin has a clear positive effect on enzymatic reaction rates.

5 Conclusion

Based on our results, it is evident that Puromycin has catalitic effects on enzymatic reactions within golgi bodies. Our HDI and ROPE values let us reject the null and claim that our test group created a difference in reaction rate. To conclude, these results may be helpful for biologists working with enzymatic reactions. Using Puromycin, they can control the reaction time of said reactions as a catalyst.

References

[1] Bates, D.M. and Watts, D.G. (1988), Nonlinear Regression Analysis and Its Applications, Wiley, Appendix A1.3.

[2] Treloar, M. A. (1974), Effects of Puromycin on Galactosyltransferase in Golgi Membranes, M.Sc. Thesis, U. of Toronto.