Nov 2018 Demetri Progress Report

Recap

Dr. Richard Kim runs a personalized medicine lab where he and his team can genotype patients to screen for genes (and other clinical covariates) which may be associated with poor metabolism of the oral anticoagulent Apixaban. A model capable of i) accurate prediction of Concentration, and ii) estimation of effect size is desired for Apixaban. To leverage information between patients and accomodate the scare sample size, I have chosen to pursue a Bayesian methodology.

Dr. Romel Tirona has graciously provided data for model development. The data consists of 36 patients measured at 8 time points after ingesting 2.5 mg of Apixaban. Each patient has two associated covariates: Sex and Disease Statues (i.e. Control or NAFLD). The model in development posists that the pharmacokinetic curve is the solution to a differential equation. The pharmacokinetic parameters are modeled as being drawn from a population distribution. The mean of this population distribution is modeled as a linear function of the covariates with log link.

In this document, I describe progress made since our last meeting in September 2018.

Exploratory Data Analysis

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## #  define BOOST_NO_CXX11_RVALUE_REFERENCES
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## #define BOOST_NO_CXX11_RVALUE_REFERENCES 1
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## /Library/Frameworks/R.framework/Versions/3.5/Resources/library/BH/include/boost/container/detail/std
## BOOST_MOVE_STD_NS_BEG
## ^
## /Library/Frameworks/R.framework/Versions/3.5/Resources/library/BH/include/boost/move/detail/std_ns_b
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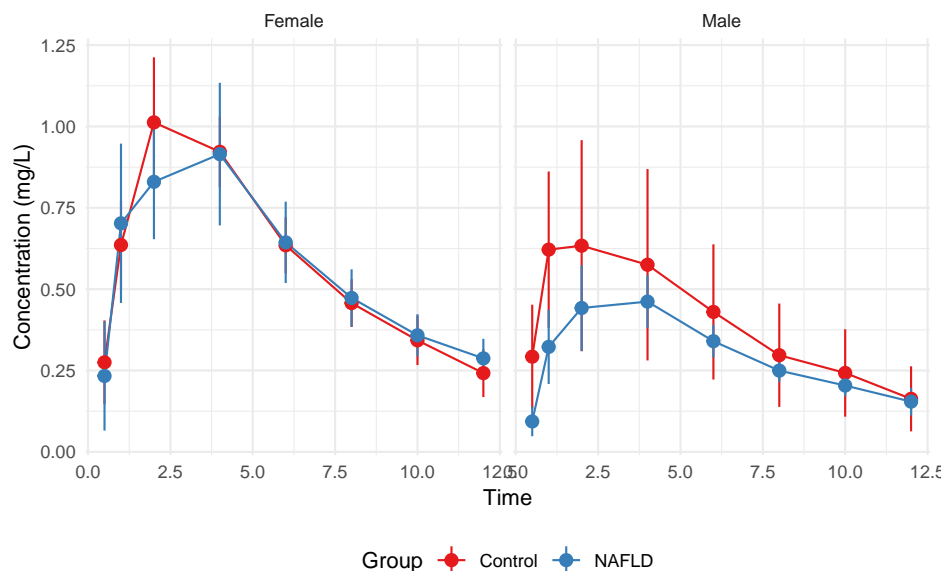
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##     #define BOOST_MOVE_STD_NS_BEG _LIBCPP_BEGIN_NAMESPACE_STD
##                                   ^
## /Applications/Xcode.app/Contents/Developer/Toolchains/XcodeDefault.xctoolchain/usr/include/c++/v1/__c
## #define _LIBCPP_BEGIN_NAMESPACE_STD namespace std {inline namespace _LIBCPP_NAMESPACE {
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## /Library/Frameworks/R.framework/Versions/3.5/Resources/library/BH/include/boost/move/detail/iterator_
## BOOST_MOVE_STD_NS_BEG
## ^
## /Library/Frameworks/R.framework/Versions/3.5/Resources/library/BH/include/boost/move/detail/std_ns_be
##     #define BOOST_MOVE_STD_NS_BEG _LIBCPP_BEGIN_NAMESPACE_STD
##                                   ^
## /Applications/Xcode.app/Contents/Developer/Toolchains/XcodeDefault.xctoolchain/usr/include/c++/v1/__c
## #define _LIBCPP_BEGIN_NAMESPACE_STD namespace std {inline namespace _LIBCPP_NAMESPACE {
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## /Library/Frameworks/R.framework/Versions/3.5/Resources/library/StanHeaders/include/stan/math/rev/cor
##     static void set_zero_all_adjoints() {
##                 ^
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## In file included from /Library/Frameworks/R.framework/Versions/3.5/Resources/library/StanHeaders/incl
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## /Library/Frameworks/R.framework/Versions/3.5/Resources/library/StanHeaders/include/stan/math/rev/cor
##     static void set_zero_all_adjoints_nested() {
##                 ^
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## /Library/Frameworks/R.framework/Versions/3.5/Resources/library/StanHeaders/include/stan/math/prim/mat
##       size_t fft_next_good_size(size_t N) {
##              ^
## 19 warnings generated.
## ld: warning: text-based stub file /System/Library/Frameworks//CoreFoundation.framework/CoreFoundatio
```

Shown below are estimated means and 95% confidence intervals for each sex and disease status. There appears
to be a large difference between sexes, with male patients having much lower concentration on average than

females. Furthermore, males suffereing from NAFLD appear to have lower concentration over time on average than male controls, but the validity of any test of hypothesis would be questionable as there are only 2 male controls.

Proposed Models

I propose a heirarchical model of apixaban metabolism. Shown below is a plate diagram. The model posits that the two covariates (sex and disease status) effect the population mean of each pharmicokinetic covariate through a log link funtion. Each patient's PK parameters are modeled as draws from this distribution. Each patient's data is then fit to a curve parameterized with these PK parameters.

Using this model allows information to be shared between patients, making the most efficient use of the data.

Results

Shown below are fits of the model to the data.

err

Time

7