

# **Variance Heterogeneity in Genetic Mapping**

Robert Wallace Corty

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Computer Science.

Chapel Hill  
2018

Approved by:

Fernando Pardo Manuel de Villena, Ph.D., chair

James Evans, M.D., Ph.D.

Yun Li, Ph.D.

Lisa Tarantino, Ph.D.

William Valdar, Ph.D.

©2018  
Robert Wallace Corty  
ALL RIGHTS RESERVED

## **ABSTRACT**

Robert Wallace Corty: Variance Heterogeneity in Genetic Mapping  
(Under the direction of William Valdar)

Lorem ipsum dolor sit amet, consetetur sadipscing elitr, sed diam nonumy eirmod tempor invidunt ut labore et dolore magna aliquyam erat, sed diam voluptua. At vero eos et accusam et justo duo dolores et ea rebum. Stet clita kasd gubergren, no sea takimata sanctus est Lorem ipsum dolor sit amet. Lorem ipsum dolor sit amet, consetetur sadipscing elitr, sed diam nonumy eirmod tempor invidunt ut labore et dolore magna aliquyam erat, sed diam voluptua. At vero eos et accusam et justo duo dolores et ea rebum. Stet clita kasd gubergren, no sea takimata sanctus est Lorem ipsum dolor sit amet. Lorem ipsum dolor sit amet, consetetur sadipscing elitr, sed diam nonumy eirmod tempor invidunt ut labore et dolore magna aliquyam erat, sed diam voluptua. At vero eos et accusam et justo duo dolores et ea rebum. Stet clita kasd gubergren, no sea takimata sanctus est Lorem ipsum dolor sit amet.

Dedication...

## ACKNOWLEDGEMENTS

Lorem ipsum dolor sit amet, consetetur sadipscing elitr, sed diam nonumy eirmod tempor invidunt ut labore et dolore magna aliquyam erat, sed diam voluptua. At vero eos et accusam et justo duo dolores et ea rebum. Stet clita kasd gubergren, no sea takimata sanctus est Lorem ipsum dolor sit amet. Lorem ipsum dolor sit amet, consetetur sadipscing elitr, sed diam nonumy eirmod tempor invidunt ut labore et dolore magna aliquyam erat, sed diam voluptua. At vero eos et accusam et justo duo dolores et ea rebum. Stet clita kasd gubergren, no sea takimata sanctus est Lorem ipsum dolor sit amet. Lorem ipsum dolor sit amet, consetetur sadipscing elitr, sed diam nonumy eirmod tempor invidunt ut labore et dolore magna aliquyam erat, sed diam voluptua. At vero eos et accusam et justo duo dolores et ea rebum. Stet clita kasd gubergren, no sea takimata sanctus est Lorem ipsum dolor sit amet.

Duis autem vel eum iriure dolor in hendrerit in vulputate velit esse molestie consequat, vel illum dolore eu feugiat nulla facilisis at vero eros et accumsan et iusto odio dignissim qui blandit praesent luptatum zzril delenit augue duis dolore te feugait nulla facilisi. Lorem ipsum dolor sit amet,

## TABLE OF CONTENTS

LIST OF TABLES .....	vii
LIST OF FIGURES .....	viii
LIST OF ABBREVIATIONS .....	ix
1 Introduction .....	1
2 Genetic Mapping in Experimental Crosses with the Double Generalized Linear Model ....	2
3 Genetic Mapping in Human Cohorts with the Double Generalized Linear Model .....	3
4 The Heteroscedastic Linear Mixed Model .....	4
4.1 Given $h^2$ , the LMM Reduces to Multiple Linear Regression .....	5
4.2 Rotation to Independence .....	6
4.3 Homoscedastic Model .....	7
4.4 Maximum Likelihood Estimation for the Heteroscedastic Model .....	7
4.4.1 Proposal .....	7
4.4.2 Validity .....	8
4.5 Simulation Results .....	9
4.6 Software .....	9
5 Conclusion and Future Directions .....	10
BIBLIOGRAPHY .....	12

## **LIST OF TABLES**

## **LIST OF FIGURES**



## LIST OF ABBREVIATIONS

QTL	quantitative trait locus
mQTL	mean-controlling quantitative trait loci
vQTL	variance-controlling quantitative trait loci
mvQTL	mean or variance controlling quantitative trait loci
LMM	Linear Mixed Model
GLS	Generalized Least Squares
SLM	Standard Linear Model
DGLM	Double Generalized Linear Model
LRT	Likelihood Ratio Test
ML	Maximum Likelihood
AYO	Add Your Own in alphabetic order. . .

CHAPTER 1

Introduction

	accommodate variance hetero- geneity	detect variance heterogeneity	handle differen- tial relatedness
LM	no	no	no
DGLM	yes	yes	no
LMM	no	no	yes
wLMM	yes	no	yes

## CHAPTER 2

# Genetic Mapping in Experimental Crosses with the Double Generalized Linear Model

Lorem ipsum dolor sit amet, consectetur adipiscing elit. Ut purus elit, vestibulum ut, placerat ac, adipiscing vitae, felis. Curabitur dictum gravida mauris. Nam arcu libero, nonummy eget, consectetur id, vulputate a, magna. Donec vehicula augue eu neque. Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Mauris ut leo. Cras viverra metus rhoncus sem. Nulla et lectus vestibulum urna fringilla ultrices. Phasellus eu tellus sit amet tortor gravida placerat. Integer sapien est, iaculis in, pretium quis, viverra ac, nunc. Praesent eget sem vel leo ultrices bibendum. Aenean faucibus. Morbi dolor nulla, malesuada eu, pulvinar at, mollis ac, nulla. Curabitur auctor semper nulla. Donec varius orci eget risus. Duis nibh mi, congue eu, accumsan eleifend, sagittis quis, diam. Duis eget orci sit amet orci dignissim rutrum.

## CHAPTER 3

# Genetic Mapping in Human Cohorts with the Double Generalized Linear Model

Lorem ipsum dolor sit amet, consectetur adipiscing elit. Ut purus elit, vestibulum ut, placerat ac, adipiscing vitae, felis. Curabitur dictum gravida mauris. Nam arcu libero, nonummy eget, consectetur id, vulputate a, magna. Donec vehicula augue eu neque. Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Mauris ut leo. Cras viverra metus rhoncus sem. Nulla et lectus vestibulum urna fringilla ultrices. Phasellus eu tellus sit amet tortor gravida placerat. Integer sapien est, iaculis in, pretium quis, viverra ac, nunc. Praesent eget sem vel leo ultrices bibendum. Aenean faucibus. Morbi dolor nulla, malesuada eu, pulvinar at, mollis ac, nulla. Curabitur auctor semper nulla. Donec varius orci eget risus. Duis nibh mi, congue eu, accumsan eleifend, sagittis quis, diam. Duis eget orci sit amet orci dignissim rutrum.

## CHAPTER 4

# The Heteroscedastic Linear Mixed Model

Whereas the previous chapters have dealt with differential relatedness obliquely, either assuming its absence or using a heuristic to correct for it, this chapter addresses it directly. The linear mixed model (LMM) [posulates] an observed phenotype,  $y$ , as the sum of five unobserved, but estimated quantities: the population mean,  $\mu$ , the fixed effect deviation,  $\mathbf{X}\beta$ , effect of the focal genetic variant(s),  $\mathbf{G}\alpha$ , the genomic value,  $\mathbf{a}$ , and the residual deviation,  $\mathbf{e}$ .

$$y = \mathbf{1}\mu + \mathbf{X}\beta + \mathbf{G}\alpha + \mathbf{a} + \mathbf{e} \quad (4.1)$$

where  $\mathbf{1}$  is a column vector of ones,  $\mathbf{X}$  is a matrix of covariates,  $\mathbf{G}$  is a design matrix of focal genetic effects, and  $\mu$ ,  $\beta$ , and  $\alpha$  are unconstrained, estimated quantities.

$\mathbf{a}$  and  $\mathbf{e}$  are so-called “random effects”, estimated in the process of model fitting, but with [constraints]. Specifically, they are modeled hierarchicclly as

$$\mathbf{a} \sim N(0, \mathbf{K}\tau^2), \quad (4.2)$$

$$\mathbf{e} \sim N(0, \mathbf{D}\sigma^2) \quad (4.3)$$

where  $\mathbf{K}$  is a known, positive semi-definite genomic similarity matrix, and  $\mathbf{D}$  is a known diagonal residual variance matrix. The scale parameters,  $\tau^2$  and  $\sigma^2$ , are constrained only in the sense that they must be non-negative.

In the context of genetic mapping, the this model is used to test whether  $\alpha = \mathbf{0}$ . If  $\alpha \neq \mathbf{0}$ , the genetic factor(s) encoded in  $\mathbf{G}$  influences the phenotype.

The two tests used to test whether  $\alpha = \mathbf{0}$ , the  $t$  test and the likelihood ratio test (LRT), require [computation] of the values of the parameters that maximize the likelihood of the data. A suite of

procedures for computing these maximum likelihood parameter values in a variety of situations was described by Henderson [cite]. The main interest of Henderson, and of the animal breeding community in general, is the “genetic value”,  $\mathbf{a}$  in the model. And it’s typically fit in the absence of  $\mathbf{G}$ , or for very few different values of  $\mathbf{G}$  for marker assisted selection.

## 4.1 Given $h^2$ , the LMM Reduces to Multiple Linear Regression

The LMM is equivalent to:

$$\mathbf{y} \sim \mathcal{N}(\mathbf{X}_c \boldsymbol{\beta}_c, \boldsymbol{\Sigma}) \quad (4.4)$$

where fixed effects design matrices are collapsed into  $\mathbf{X}$  and the variance-covariance matrices of the random effects are combined into  $\boldsymbol{\Sigma}$ . Specifically,

$$\mathbf{X}_c = [\mathbf{1} \quad \mathbf{X} \quad \mathbf{G}] \quad (4.5)$$

$$\boldsymbol{\beta}_c = [\mu \quad \boldsymbol{\beta}^T \quad \boldsymbol{\alpha}^T]^T \quad (4.6)$$

$$\boldsymbol{\Sigma} = \mathbf{K}\tau^2 + \mathbf{D}\sigma^2 \quad (4.7)$$

Going forward, we refer to  $\mathbf{X}_c$  and  $\boldsymbol{\beta}_c$  as simply  $\mathbf{X}$  and  $\boldsymbol{\beta}$  for simplicity.

This model can be reparametrized to directly use the well-known narrow sense heritability, increasing its interpretability. Specifically,  $h^2 = \frac{\tau^2}{\tau^2 + \sigma^2}$  and  $\lambda = \tau^2 + \sigma^2$ .

$$\boldsymbol{\Sigma} = \left( \mathbf{K} \frac{\tau^2}{\tau^2 + \sigma^2} + \mathbf{D} \frac{\sigma^2}{\tau^2 + \sigma^2} \right) (\tau^2 + \sigma^2) \quad (4.8)$$

$$= \mathbf{K}h^2 + \mathbf{D}(1 - h^2)\lambda \quad (4.9)$$

Thus, for any given value of  $h^2$ , we can define  $\mathbf{V} = \mathbf{K}h^2 + \mathbf{D}(1 - h^2)$ , and the LMM reduces to a standard linear model (SLM):

$$\mathbf{y} \sim \mathcal{N}(\mathbf{X}\boldsymbol{\beta}, \mathbf{V}\lambda) \quad (4.10)$$

This SLM has log likelihood:

$$\ell(\boldsymbol{\beta}, \lambda; \mathbf{y}, \mathbf{X}, \mathbf{V}) = -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\mathbf{V}\lambda| - \frac{1}{2\lambda} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^T \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta}) \quad (4.11)$$

$$= -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\mathbf{V}| - \frac{n}{2} \log \lambda - \frac{1}{2\lambda} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^T \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta}) \quad (4.12)$$

And there is a known, closed-form, maximum likelihood estimator for its two parameters:

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{V}^{-1} \mathbf{y} \quad (4.13)$$

$$\hat{\lambda} = \left\| (\mathbf{X}\hat{\boldsymbol{\beta}} - \mathbf{y})^T (\mathbf{X}\hat{\boldsymbol{\beta}} - \mathbf{y}) \right\|_2 \quad (4.14)$$

In the context of a genome scan, we want to calculate these maximum likelihood estimators for a single phenotype,  $\mathbf{y}$ , genomic similarity,  $\mathbf{K}$  residual variance,  $\mathbf{D}$ , and many different values of  $\mathbf{X}$  — recall that the genetic variant(s) being investigated are in  $\mathbf{G}$ . Also recall that, though we have described a parameterization that recapitulates a standard linear regression problem when  $h^2$  is known, we do not, in general know the true value of  $h^2$ , so we will additionally want to optimize over all possible values of  $h^2 \in [0, 1]$ .

We now describe a matrix algebra trick that increases the up-front computational cost of fitting the linear regression model Equation 4.10, but drastically decreases the computational cost for each new value of  $\mathbf{X}$ .

## 4.2 Rotation to Independence

Imagine we knew of a multiplier matrix,  $\mathbf{M}$  such that

$$\mathbf{M}^T \mathbf{M} = \mathbf{V}^{-1} \quad (4.15)$$

Let us now consider a new, rotated phenotype vector,  $\mathbf{y}_r = \mathbf{M}\mathbf{y}$ , a new covariate matrix,  $\mathbf{X}_r = \mathbf{M}\mathbf{X}$ , and a new SLM.

$$\mathbf{y}_r \sim \mathcal{N}(\mathbf{X}_r \boldsymbol{\beta}_r, \mathbf{I} \lambda_r) \quad (4.16)$$

The log likelihood of this SLM is:

$$\ell(\boldsymbol{\beta}_r, \lambda_r; \mathbf{X}_r, \mathbf{y}_r) = -\frac{n}{2} \log(2\pi) - \frac{1}{2} \log |\mathbf{I}| - \frac{n}{2} \log \lambda_r - \frac{1}{2\lambda_r} (\mathbf{y}_r - \mathbf{X}_r \boldsymbol{\beta}_r)^T (\mathbf{y}_r - \mathbf{X}_r \boldsymbol{\beta}_r) \quad (4.17)$$

$$= -\frac{n}{2} \log(2\pi) - \frac{n}{2} \log \lambda_r - \frac{1}{2\lambda_r} (\mathbf{M}\mathbf{y} - \mathbf{M}\mathbf{X}\boldsymbol{\beta})^T (\mathbf{M}\mathbf{y} - \mathbf{M}\mathbf{X}\boldsymbol{\beta}) \quad (4.18)$$

$$= -\frac{n}{2} \log(2\pi) - \frac{n}{2} \log \lambda_r - \frac{1}{2\lambda_r} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^T \mathbf{M}^T \mathbf{M} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta}) \quad (4.19)$$

$$= -\frac{n}{2} \log(2\pi) - \frac{n}{2} \log \lambda_r - \frac{1}{2\lambda_r} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^T \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta}) \quad (4.20)$$

and its ML estimators are:

$$\widehat{\boldsymbol{\beta}}_r = (\mathbf{X}_r^T \mathbf{X}_r)^{-1} \mathbf{X}_r^T \mathbf{y}_r \quad (4.21)$$

$$\widehat{\lambda}_r = \left\| (\mathbf{X}_r \widehat{\boldsymbol{\beta}}_r - \mathbf{y}_r)^T (\mathbf{X}_r \widehat{\boldsymbol{\beta}}_r - \mathbf{y}_r) \right\|_2 \quad (4.22)$$

Thus we have established that, given  $\mathbf{M}$  we can fit the model

### 4.3 Homoscedastic Model

[D = I] Kang proposed the following [cite EMMA].

### 4.4 Maximum Likelihood Estimation for the Heteroscedastic Model

The above  $\mathbf{M}$  relied on [point out where D=I is required] [in step X]. Generally, however, some phenotypes are known with more certainty than others. Want to have a diagonal D, but not necessarily I.

#### 4.4.1 Proposal

$$\mathbf{M} = (\boldsymbol{\Lambda}_L + \delta \mathbf{I})^{-\frac{1}{2}} \mathbf{U}_L^T \mathbf{D}^{-\frac{1}{2}} \quad (4.23)$$



where

$$\mathbf{L} = \mathbf{D}^{-\frac{1}{2}} \mathbf{K} \mathbf{D}^{-\frac{1}{2}} \quad (4.24)$$

and

$$\mathbf{L} = \mathbf{U}_L \mathbf{\Lambda}_L \mathbf{U}_L^T \quad (4.25)$$

is its eigen decomposition

#### 4.4.2 Validity

To be a valid multiplier matrix,  $\mathbf{M}$  must have the property:

$$\mathbf{M}^T \mathbf{M} = \mathbf{V}^{-1}$$

*Proof.* First, derive a useful form of  $\mathbf{V}$ .

$\begin{aligned} \mathbf{V} &= \mathbf{K} + \delta \mathbf{D} \\ &= \mathbf{D}^{\frac{1}{2}} \mathbf{D}^{-\frac{1}{2}} (\mathbf{K} + \delta \mathbf{D}) \\ &= \mathbf{D}^{\frac{1}{2}} \mathbf{D}^{-\frac{1}{2}} (\mathbf{K} + \delta \mathbf{D}) \mathbf{D}^{-\frac{1}{2}} \mathbf{D}^{\frac{1}{2}} \\ &= \mathbf{D}^{\frac{1}{2}} (\mathbf{D}^{-\frac{1}{2}} \mathbf{K} \mathbf{D}^{-\frac{1}{2}} + \delta \mathbf{D}^{-\frac{1}{2}} \mathbf{D} \mathbf{D}^{-\frac{1}{2}}) \mathbf{D}^{\frac{1}{2}} \\ &= \mathbf{D}^{\frac{1}{2}} (\mathbf{D}^{-\frac{1}{2}} \mathbf{K} \mathbf{D}^{-\frac{1}{2}} + \delta \mathbf{I}) \mathbf{D}^{\frac{1}{2}} \\ &= \mathbf{D}^{\frac{1}{2}} (\mathbf{L} + \delta \mathbf{I}) \mathbf{D}^{\frac{1}{2}} \\ &= \mathbf{D}^{\frac{1}{2}} (\mathbf{U}_L \mathbf{\Lambda}_L \mathbf{U}_L^T + \delta \mathbf{I}) \mathbf{D}^{\frac{1}{2}} \\ &= \mathbf{D}^{\frac{1}{2}} (\mathbf{U}_L \mathbf{\Lambda}_L \mathbf{U}_L^T + \delta \mathbf{U}_L \mathbf{U}_L^T) \mathbf{D}^{\frac{1}{2}} \\ &= \mathbf{D}^{\frac{1}{2}} \mathbf{U}_L (\mathbf{\Lambda}_L + \delta \mathbf{I}) \mathbf{U}_L^T \mathbf{D}^{\frac{1}{2}} \end{aligned}$	<p>definition</p> <p>pre-multiply by <math>\mathbf{D}^{\frac{1}{2}} \mathbf{D}^{-\frac{1}{2}} = \mathbf{I}</math></p> <p>post-multiply by <math>\mathbf{D}^{-\frac{1}{2}} \mathbf{D}^{\frac{1}{2}} = \mathbf{I}</math></p> <p>distribute <math>\mathbf{D}^{-\frac{1}{2}}</math> in</p> <p>definition of root inverse</p> <p>define: <math>\mathbf{L} = \mathbf{D}^{-\frac{1}{2}} \mathbf{K} \mathbf{D}^{-\frac{1}{2}}</math></p> <p>eigen decomposition of <math>\mathbf{L}</math></p> <p>property of eigen vectors</p> <p>distributive property</p>
--	--

and invert it

$$\begin{aligned}
\mathbf{V}^{-1} &= \left( \mathbf{D}^{\frac{1}{2}} \mathbf{U}_L (\mathbf{\Lambda}_L + \delta \mathbf{I}) \mathbf{U}_L^T \mathbf{D}^{\frac{1}{2}} \right)^{-1} && \text{definition} \\
&= \left( \mathbf{D}^{\frac{1}{2}} \right)^{-1} \left( \mathbf{U}_L (\mathbf{\Lambda}_L + \delta \mathbf{I}) \mathbf{U}_L^T \right)^{-1} \left( \mathbf{D}^{\frac{1}{2}} \right)^{-1} && \text{inverse of product} \\
&= \mathbf{D}^{-\frac{1}{2}} \left( \mathbf{U}_L (\mathbf{\Lambda}_L + \delta \mathbf{I}) \mathbf{U}_L^T \right)^{-1} \mathbf{D}^{-\frac{1}{2}} && \text{inverse of diagonal matrix} \\
&= \mathbf{D}^{-\frac{1}{2}} \mathbf{U}_L (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-1} \mathbf{U}_L^T \mathbf{D}^{-\frac{1}{2}} && \text{inverse of eigen decomposition}
\end{aligned}$$

and compare to  $\mathbf{M}^T \mathbf{M}$

$$\begin{aligned}
\mathbf{M}^T \mathbf{M} &= \left( (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-\frac{1}{2}} \mathbf{U}_L^T \mathbf{D}^{-\frac{1}{2}} \right)^T \left( (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-\frac{1}{2}} \mathbf{U}_L^T \mathbf{D}^{-\frac{1}{2}} \right) && \text{definition} \\
&= \left( \mathbf{D}^{-\frac{1}{2}} \mathbf{U}_L (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-\frac{1}{2}} \right) \left( (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-\frac{1}{2}} \mathbf{U}_L^T \mathbf{D}^{-\frac{1}{2}} \right) && \text{transpose of product} \\
&= \mathbf{D}^{-\frac{1}{2}} \mathbf{U}_L \left( (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-\frac{1}{2}} (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-\frac{1}{2}} \right) \mathbf{U}_L^T \mathbf{D}^{-\frac{1}{2}} && \text{associative property} \\
&= \mathbf{D}^{-\frac{1}{2}} \mathbf{U}_L (\mathbf{\Lambda}_L + \delta \mathbf{I})^{-1} \mathbf{U}_L^T \mathbf{D}^{-\frac{1}{2}} && \text{definition of root inverse}
\end{aligned}$$

□

## 4.5 Simulation Results

## 4.6 Software

## CHAPTER 5

# Conclusion and Future Directions

Lorem ipsum dolor sit amet, consectetur adipiscing elit. Ut purus elit, vestibulum ut, placerat ac, adipiscing vitae, felis. Curabitur dictum gravida mauris. Nam arcu libero, nonummy eget, consectetur id, vulputate a, magna. Donec vehicula augue eu neque. Pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Mauris ut leo. Cras viverra metus rhoncus sem. Nulla et lectus vestibulum urna fringilla ultrices. Phasellus eu tellus sit amet tortor gravida placerat. Integer sapien est, iaculis in, pretium quis, viverra ac, nunc. Praesent eget sem vel leo ultrices bibendum. Aenean faucibus. Morbi dolor nulla, malesuada eu, pulvinar at, mollis ac, nulla. Curabitur auctor semper nulla. Donec varius orci eget risus. Duis nibh mi, congue eu, accumsan eleifend, sagittis quis, diam. Duis eget orci sit amet orci dignissim rutrum.

Nam dui ligula, fringilla a, euismod sodales, sollicitudin vel, wisi. Morbi auctor lorem non justo. Nam lacus libero, pretium at, lobortis vitae, ultricies et, tellus. Donec aliquet, tortor sed accumsan bibendum, erat ligula aliquet magna, vitae ornare odio metus a mi. Morbi ac orci et nisl hendrerit mollis. Suspendisse ut massa. Cras nec ante. Pellentesque a nulla. Cum sociis natoque penatibus et magnis dis parturient montes, nascetur ridiculus mus. Aliquam tincidunt urna. Nulla ullamcorper vestibulum turpis. Pellentesque cursus luctus mauris.

Nulla malesuada porttitor diam. Donec felis erat, congue non, volutpat at, tincidunt tristique, libero. Vivamus viverra fermentum felis. Donec nonummy pellentesque ante. Phasellus adipiscing semper elit. Proin fermentum massa ac quam. Sed diam turpis, molestie vitae, placerat a, molestie nec, leo. Maecenas lacinia. Nam ipsum ligula, eleifend at, accumsan nec, suscipit a, ipsum. Morbi blandit ligula feugiat magna. Nunc eleifend consequat lorem. Sed lacinia nulla vitae enim. Pellentesque tincidunt purus vel magna. Integer non enim. Praesent euismod nunc eu purus. Donec

bibendum quam in tellus. Nullam cursus pulvinar lectus. Donec et mi. Nam vulputate metus eu enim. Vestibulum pellentesque felis eu massa.

Quisque ullamcorper placerat ipsum. Cras nibh. Morbi vel justo vitae lacus tincidunt ultrices. Lorem ipsum dolor sit amet, consectetur adipiscing elit. In hac habitasse platea dictumst. Integer tempus convallis augue. Etiam facilisis. Nunc elementum fermentum wisi. Aenean placerat. Ut imperdiet, enim sed gravida sollicitudin, felis odio placerat quam, ac pulvinar elit purus eget enim. Nunc vitae tortor. Proin tempus nibh sit amet nisl. Vivamus quis tortor vitae risus porta vehicula.

## **BIBLIOGRAPHY**