

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/66031> holds various files of this Leiden University dissertation.

**Author:** Balan, T.A.

**Title:** Advances in frailty models

**Issue Date:** 2018-09-26

# **Advances in Frailty Models**

Theodor Adrian Bălan

Cover design: Alexandru Andrei  
Printing: Ipskamp Printing, The Netherlands

©2018 Theodor Adrian Bălan, Leiden, The Netherlands.  
All rights reserved. No part of this publication may be reproduced without prior permission of the author.

ISBN: 978-90-9031062-6

# Advances in Frailty Models

PROEFSCHRIFT

ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van de Rector Magnificus prof.mr. C.J.J.M. Stolker,  
volgens besluit van het College voor Promoties  
te verdedigen op woensdag 26 september 2018  
klokke 13.45 uur

door

Theodor Adrian Bălan  
geboren te Boekarest, Roemenië in 1989

Promotor: Prof. dr. H. Putter

Leden promotiecommissie: Prof. dr. S. le Cessie  
Prof. dr. M.J.C. Eijkemans  
· *Universitair Medisch Centrum Utrecht, Utrecht*  
Prof. dr. D. Rizopoulos  
· *Erasmus Medisch Centrum, Rotterdam*

---

---

# TABLE OF CONTENTS

---

<b>Table of Contents</b>	<b>v</b>
<b>1 Introduction: A tutorial in frailty modeling</b>	<b>1</b>
1.1 Introduction . . . . .	1
1.2 Univariate frailty models . . . . .	3
1.2.1 Heterogeneity in the Cox model . . . . .	3
1.2.2 The frailty model . . . . .	6
1.2.3 Frailty distributions . . . . .	7
1.2.4 Frailty effects . . . . .	10
1.2.5 Identifiability . . . . .	13
1.3 Shared frailty models . . . . .	14
1.3.1 Missing covariates in paired data . . . . .	14
1.3.2 Clustered failures . . . . .	15
1.3.3 Frailty model for recurrent events . . . . .	21
1.4 Frailty models in practice . . . . .	22
1.4.1 Estimation and inference . . . . .	22
1.4.2 Software . . . . .	25
1.4.3 Data representation . . . . .	25
1.5 Extensions . . . . .	27
1.6 Outline of the thesis . . . . .	28
<b>2 Non-proportional hazards and unobserved heterogeneity in clustered survival data: When can we tell the difference?</b>	<b>29</b>
2.1 Introduction . . . . .	30
2.2 Models . . . . .	31
2.2.1 Proportional hazards models . . . . .	31
2.2.2 Frailty models . . . . .	32

2.2.3	Non-proportional hazards . . . . .	33
2.3	Simulation study . . . . .	35
2.3.1	General framework . . . . .	35
2.3.2	Likelihood Ratio Test . . . . .	37
2.3.3	Commenges-Andersen test . . . . .	40
2.3.4	Estimated frailty variance . . . . .	43
2.3.5	Cumulative hazard . . . . .	43
2.4	Application . . . . .	43
2.5	Conclusion . . . . .	47
<b>3</b>	<b>Score test for association between recurrent events and a terminal event</b>	<b>53</b>
3.1	Introduction . . . . .	53
3.2	Models . . . . .	55
3.3	Tests for independence . . . . .	57
3.3.1	Score Test . . . . .	57
3.3.2	Alternative tests . . . . .	59
3.4	Simulation . . . . .	60
3.5	Application . . . . .	62
3.6	Discussion . . . . .	67
<b>4</b>	<b>Ascertainment correction in frailty models for recurrent events data</b>	<b>71</b>
4.1	Introduction . . . . .	71
4.2	Methods . . . . .	73
4.2.1	Statistical models . . . . .	73
4.2.2	Ascertainment adjustment . . . . .	75
4.2.3	Estimation of $\lambda_0$ . . . . .	78
4.3	Simulation study . . . . .	80
4.3.1	Toy example . . . . .	80
4.3.2	Set up . . . . .	81
4.3.3	Simulation results . . . . .	84
4.3.4	Incomplete history . . . . .	92
4.4	Data analysis . . . . .	92
4.5	Discussion . . . . .	98
<b>5</b>	<b>frailtyEM: An R Package for Estimating Semiparametric Shared Frailty Models</b>	<b>103</b>
5.1	Introduction . . . . .	104
5.2	Model . . . . .	105
5.2.1	Shared frailty models . . . . .	105
5.2.2	Likelihood . . . . .	107
5.2.3	Ascertainment and left truncation . . . . .	108
5.2.4	Analysis and quantities of interest . . . . .	110
5.2.5	Goodness of fit . . . . .	111

---

5.3	Estimation and implementation . . . . .	111
5.3.1	Syntax . . . . .	111
5.3.2	Profile EM algorithm . . . . .	112
5.3.3	Standard errors and confidence intervals . . . . .	113
5.3.4	Methods . . . . .	114
5.3.5	Plotting and additional features . . . . .	114
5.4	Illustration . . . . .	115
5.4.1	CGD . . . . .	115
5.4.2	Kidney . . . . .	120
5.4.3	Rats data . . . . .	123
5.5	Conclusion . . . . .	125
	<b>References</b>	<b>131</b>
	<b>English Summary</b>	<b>139</b>
	<b>Nederlandse Samenvatting</b>	<b>145</b>
	<b>Acknowledgements</b>	<b>153</b>
	<b>Curriculum Vitae</b>	<b>155</b>



