MULTISCALE MODELING OF HUMAN ADDICTION: A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS AND HEALING

A Dissertation Presented

by

YARIV Z. LEVY

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 2013

Computer Science

© Copyright by Yariv Z. Levy 2013

All Rights Reserved

MULTISCALE MODELING OF HUMAN ADDICTION: A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS AND HEALING

A Dissertation Presented

by

YARIV Z. LEVY

Approved as to style and content by:

_____
Andrew G. Barto, co-Chair

_____
Jerrold S. Meyer, co-Chair

_____
Sridhar Mahadevan, Member

_____
Neil E. Berthier, Member

_____
Lori A. Clarke, Department Chair
Computer Science

DEDICATION

To my parents,

to my family,

and to my friends.

ACKNOWLEDGMENTS

I express my deepest gratitude to my co-Advisors, Professor Andrew G. Barto and Professor Jerrold S. Meyer. Professor Barto taught me why essence is the most elegant art of science, and Professor Meyer planted the seeds which bloomed.

I am grateful to the other members of my committee, Professor Sridhar Mahadevan and Professor Neil E. Berthier. Professor Mahadevan encouraged me to be meticulous, and Professor Berthier showed me how a good question can lead to a better answer.

I also express my deepest gratitude to Professor Dino J. Levy who taught me the fundamentals of drug addiction and encouraged me throughout my work. I was also guided and encouraged by Professor Hava T. Siegelmann during the early stages of my research.

I was fortunate to meet and interact with many colleagues, fellows, and teammates during the course of my stay at University of Massachusetts Amherst. I thank them for their curiosity, encouragement, and support.

I wish to thank the staff of the Department and of the University, including the Computer Science Administrative assistants, the Computer Science Computing Facility, the UMass Amherst Libraries, and the UMass Physical Plant Division. Their help was essential for successful completion of my PhD.

My work was supported in part by the National Science Foundation under NSF Grant #CNS-0619337. Any opinions, findings, conclusions or recommendations expressed here are the author's and do not necessarily reflect those of the sponsor.

ABSTRACT

MULTISCALE MODELING OF HUMAN ADDICTION: A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS AND HEALING

FEBRUARY 2013

YARIV Z. LEVY

B.Sc., ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE

M.Sc., ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE

Ph.D., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Professor Andrew G. Barto and Professor Jerrold S. Meyer

This dissertation presents a computational multiscale framework for predicting behavioral tendencies related to human addiction. The research encompasses three main contributions. The first contribution presents a formal, heuristic, and exploratory framework to conduct interdisciplinary investigations about the neuropsychological, cognitive, behavioral, and recovery constituents of addiction. The second contribution proposes a computational framework to account for real-life recoveries that are not dependent on pharmaceutical, clinical, and counseling support. This exploration relies upon a combination of current biological beliefs together with unorthodox rehabilitation practices, such as meditation, and proposes a conjecture regarding possible cognitive mechanisms involved in the recovery process. Further elaboration of this investigation leads on to the third contribution, which introduces a computational hypothesis for exploring the allostatic theory of addiction. A person engaging in drug

consumption is likely to encounter mood deterioration and eventually to suffer the loss of a reasonable functional state (e.g., experience depression). The allostatic theory describes how the consumption of abusive substances modifies the brain's reward system by means of two mechanisms which aim to viably maintain the functional state of an addict. The first mechanism is initiated in the reward system itself, whereas the second might originate in the endocrine system or elsewhere. The proposed computational hypothesis indicates that the first mechanism can explain the functional stabilization of the addict, whereas the second mechanism is a candidate for a source of possible recovery.

The formal arguments presented in this dissertation are illustrated by simulations which delineate archetypal patterns of human behavior toward drug consumption: escalation of use and influence of conventional and alternative rehabilitation treatments. Results obtained from this computational framework encourage an integrative approach to drug rehabilitation therapies which combine conventional therapies with alternative practices to achieve higher rates of consumption cessation and lower rates of relapse.

TABLE OF CONTENTS

Page

ACKNOWLEDGMENTS v

ABSTRACT vii

LIST OF TABLES xii

LIST OF FIGURES xiii

CHAPTER

1. INTRODUCTION 1

    1.1 Historical account of addiction in humankind 4
    1.2 Maturing out of addiction and natural recoveries 8
    1.3 Contributions 10

2. BACKGROUND: BIOLOGICAL MODELS OF ADDICTION 14

    2.1 The physical dependence model 16
    2.2 The positive reinforcement model 18
    2.3 The incentive-sensitization model 19
    2.4 The opponent-process model 20
    2.5 The allostatic model 21
    2.6 The disease model 24
    2.7 The impaired response inhibition and salience attribution model 27

3. RELATED WORK: COMPUTATIONAL MODELS OF ADDICTION 29

    3.1 Epidemiological models 30
    3.2 Economic models 32
    3.3 Quantitative pharmacological models 35
    3.4 Abstract models of dopamine functions 36
    3.5 Knowledge repository models 39
    3.6 Relations to the model advanced in this dissertation 43

4. FIVE-STEPS TOWARD A COMPUTATIONAL MODEL 48

    4.1 Formalization of the biology underlying addiction 50
    4.2 Demonstration of expandability 51

4.3 Qualitative validation 53
4.4 Dynamical properties analysis 54
4.5 Sensitivity analysis 56
4.6 Concluding remarks 58

5. HYPOTHESIS-DRIVEN FRAMEWORK FOR MATURING OUT 60

5.1 A Multiscale Model of Addiction 60
5.2 Methods 64

5.2.1 Probability of a recovery process 66

5.3 Results: plausible scenarios of drug-seeking and maturing out 69

5.3.1 Baseline simulations 69
5.3.2 Direct Influence of the Recovery Process 70
5.3.3 Direct and Potentially Long-Term Influences of the Recovery Process 70

5.4 Analysis: a cognitive learning mechanism to enable maturing out 75
5.5 Concluding Remarks 78

6. A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS 81

6.1 Introduction 82
6.2 Methods: Computational framework for allostasis 85

6.2.1 Model validation and provisional assumption 91

6.3 Results 92

6.3.1 Baseline: constant reward set point and constant baseline reward threshold 94
6.3.2 Case Study 1: Allostatic state trajectory during escalation of drug consumption 97
6.3.3 Case Study 2: Allostatic state trajectory during conventional therapies 99
6.3.4 Case Study 3: Allostatic state trajectory during alternative medical treatments 101

6.4 Concluding remarks 110

7. DISCUSSION AND CONCLUSION 111

7.1 Biological conjectures and limitations 112
7.2 The model's high dimensionality 114
7.3 Conclusion: implications for treatments 116

APPENDICES

A. SUPPLEMENTARY METHODS 120
B. SUPPLEMENTARY FIGURES 129
C. SUPPLEMENTARY TABLE 148

BIBLIOGRAPHY 148

LIST OF TABLES

Table Page

Table 1: Data about the US narcotics users population in 1955 and the related former addicts population at the end of 1959 68

Table 2: Values of the parameters as used in Figures 13 to 37 148

LIST OF FIGURES

Figure Page

Figure 1: Neuropsychological, cognitive, behavioral and recovery scales are the four aspects considered in mathematical and computational models of addiction 2

Figure 2: Recapitulation of 10 investigations of maturing out from heroin addiction undertaken between 1962-1980 9

Figure 3: Epidemiological, economic, pharmacological, dopaminergic, and knowledge repository models of addiction are mostly concerned with two scales of observations 30

Figure 4: The knowledge repository (KR) model presented in this dissertation takes into account the four scales of observations considered in previous formal models of addiction 49

Figure 5: Prior to execution, the model's phenomenological and mathematical inter-correlations were analyzed, and when necessary a functional control was crafted and refined by analysis of the model's output 57

Figure 6: Diagram of the computational model, where the output of the model $G(t)$ represents the tendency for drug-seeking behavior 63

Figure 7: Mean and standard errors of the mean for 100 simulations of B.T.'s profile at 35 years old, 600 time steps long (25 days) without any effect of $h(t)$ 72

Figure 8: Mean and standard errors of the mean for 100 simulations of B.T.'s profile at 35 years old, 600 time steps long (25 days) under the direct effect of $h(t)$ 73

Figure 9: Mean and standard errors of the mean for 100 simulations of B.T.'s profile at 35 years old, 600 time steps long (25 days) under the effect of $h(t)$ 74

Figure 10: Simulations of a virtual subject having different cognitive inclinations 76

Figure 11: Comparison of simulations using the original and the cognitively unbiased values of γ 80

Figure 12: Diagram of the computational model. Time units differ: t is in minutes and t^* in hours. Output $M(t)$ is the mood estimation within the allostatic framework 84

Figure 13: Baseline (T_S and T_0 are constant) 96

Figure 14: Case Study 1 (cognitive weights and reward components) 104

Figure 15: Case Study 1 (mood and health state assessments) 105

Figure 16: Case Study 2 (cognitive weights and reward components) 106

Figure 17: Case Study 2 (mood and health state assessments) 107

Figure 18: Case Study 3 (cognitive weights and reward components) 108

Figure 19: Case Study 3 (mood and health state assessments) 109

Figure 20: Details of the baseline presented in Figure 13 130

Figure 21: Details of Case Study 1 presented in Figures 14 and 15 131

Figure 22: Comparison of different probabilities defining the associative learning between the drug and its pleasurable effect 132

Figure 23: Details of simulations presented in Figure 22 133

Figure 24: Details of Case Study 2 presented in Figures 16 and 17 134

Figure 25: Comparison of different probabilities defining the durability of H for conventional therapies, with both T_S and T_0 time-dependent 135

Figure 26: Details of simulations presented in Figure 25 136

Figure 27: Comparison of different probabilities defining the durability of H for conventional therapies, with T_S constant 137

Figure 28: Details of simulations presented in Figure 27 138

Figure 29: Comparison of different probabilities defining the durability of H for conventional therapies, with T_0 constant 139

Figure 30: Details of simulations presented in Figure 29 140

Figure 31: Details of Case Study 3 presented in Figures 18 and 19 141

Figure 32: Comparison of different probabilities defining the durability of H for alternative treatments, with both T_S and T_0 time-dependent 142

Figure 33: Details of simulations presented in Figure 32 143

Figure 34: Comparison of different probabilities defining the durability of H for alternative treatments, with T_S constant 144

Figure 35: Details of simulations presented in Figure 34 145

Figure 36: Comparison of different probabilities defining the durability of H for alternative treatments, with T_0 constant 146

Figure 37: Details of simulations presented in Figure 36 147