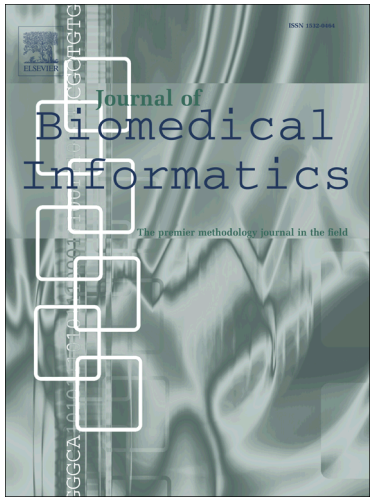

A Model-driven methodology for exploring complex disease comorbidities applied to autism spectrum disorder and inflammatory bowel disease

Judith Somekh, Mor Peleg, Alal Eran, Itay Koren, Ariel Feiglin, Alik Demishtein, Ruth Shiloh, Monika Heiner, Sek Won Kong, Zvulun Elazar, Isaac Kohane

PII: S1532-0464(16)30085-5
DOI: http://dx.doi.org/10.1016/j.jbi.2016.08.008
Reference: YJBIN 2616

To appear in: *Journal of Biomedical Informatics*

Received Date: 29 January 2016
Revised Date: 29 July 2016
Accepted Date: 5 August 2016

Please cite this article as: Somekh, J., Peleg, M., Eran, A., Koren, I., Feiglin, A., Demishtein, A., Shiloh, R., Heiner, M., Kong, S.W., Elazar, Z., Kohane, I., A Model-driven methodology for exploring complex disease comorbidities applied to autism spectrum disorder and inflammatory bowel disease, *Journal of Biomedical Informatics* (2016), doi: http://dx.doi.org/10.1016/j.jbi.2016.08.008

A Model-driven methodology for exploring complex disease comorbidities applied to autism spectrum disorder and inflammatory bowel disease

Judith Somekh[1,2]*, Mor Peleg[2], Alal Eran[1,7,9], Itay Koren[3], Ariel Feiglin[1], Alik Demishtein[4], Ruth Shiloh[5], Monika Heiner[6], Sek Won Kong[7], Zvulun Elazar[4], Isaac Kohane[1,7,8]

[1]*Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts, USA*
[2]*Department of Information Systems, University of Haifa, Haifa, Israel*
[3]*Department of Genetics, Harvard Medical School; Division of Genetics, Brigham and Women's Hospital; Howard Hughes Medical Institute, Boston, Massachusetts, USA*
[4]*Department of Biological Chemistry, Weizmann Institute of Science, Rehovot, Israel*
[5]*Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel*
[6]*Computer Science Institute, Brandenburg University of Technology, Cottbus, Germany*
[7]*Computational Health Informatics Program, Boston Children's Hospital, Boston, Massachusetts, USA*
[8]*Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA*
[9]*Department of Life Sciences, Ben Gurion University, Beer Sheva, Israel*

**corresponding author: Judith_somekh@hms.harvard.edu*

Keywords
Petri nets; Modeling; Autism; IBD; ASD; Autophagy

Abstract
We propose a model-driven methodology aimed to shed light on complex disorders. Our approach enables exploring shared etiologies of comorbid diseases at the molecular pathway level. The method, Comparative Comorbidities Simulation (CCS), uses stochastic Petri net simulation for examining the phenotypic effects of perturbation of a network known to be involved in comorbidities to predict new roles for mutations in comorbid conditions. To demonstrate the utility of our novel methodology, we investigated the molecular convergence of autism spectrum disorder (ASD) and inflammatory bowel disease (IBD) on the autophagy pathway. In addition to validation by domain experts, we used formal analyses to demonstrate the model's self-consistency. We then used CCS to compare the effects of loss of function (LoF) mutations previously implicated in either ASD or IBD on the autophagy pathway. CCS identified similar dynamic consequences of these mutations in the autophagy pathway. Our method suggests that two LoF mutations previously implicated in IBD may contribute to ASD,