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Secondary Analysis of Concussion Data

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- ABSTRACT: Clinical studies are expensive & time-consuming. Typically in these studies specific hypotheses are subjected to confirmatory test. Yet the data may harbor evidence of unanticipated relations between variables. It is thus desirable to subject the data to secondary analyses in the hope of discovering novel & valuable associations. Exploratory analysis, however, is tentative: findings should be replicated in new data.
- This presentation reports some secondary analyses on concussion data. Data mining on 2 datasets will be discussed, & some unexpected findings reported. The analyses use reconstructability analysis (RA), a probabilistic graphical modeling method implemented in the Occam software package developed in the SySc Program, which is first briefly described.

1. Exploratory modeling with RA (Occam)

2. Sample results on Preece, Wright data sets

- Stephanie Kolakowsky-Hayner, Brain Trauma Foundation: Brain Trauma Evidence-Based Consortium (BTEC) project head
  - Maya Balamane, Assistant Program Manager
- Nancy Carney, OHSU, SySc-Psychology PhD: BTEC founder & previous head;
  - Tracie Nettleton, Research assistant
- BTEC funded by DoD via BTF & Stanford

- **PSU BTEC Project**
  - Wayne Wakeland, PI of overall project
  - & PI of **Dynamic Model Initiative Subproject**
- **Data Analytics (Occam) Subproject**
  - Martin Zwick, co-PI; Forrest Alexander, Peter Olson, Programmers

1. Exploratory modeling with RA (Occam)

- Exploratory modeling (data mining) with Reconstructability Analysis (RA):
  - to contribute to a clinically-useful TBI classification system & other BTEC projects
  - to extract additional information from past studies
  - to enhance RA methodology & Occam implementation for future data sets

Rationale for exploratory modeling

- Most studies are confirmatory, testing only specific hypotheses. Since studies are expensive & time-consuming, it is useful to explore what else might be discovered in the data.
- Exploratory studies can find *unexpected* non-linear & many-variable interaction effects (which should then be tested in confirmatory mode with new data).
- Exploratory studies (by data analysts) are unbiased.

Why RA & Occam software

- Explicitly designed for exploratory modeling
  - Analyzes both nominal & continuous (binned) variables
  - Easily interpretable; standard text input; web-accessible, emails results to user; available for research use

- Other statistical & machine-learning methods (log-linear, logistic regression, Bayesian networks, classification trees, support vector machines, neural nets) not well designed for exploration, *or* have limited model types, *or* have difficulty with nominal variables or with stochasticity

PAST/PRESENT RA APPLICATIONS

- *BIOMEDICAL*

  Gene-disease association, disease risk factors, gene expression, health care use & outcomes, dementia, diabetes, heart disease, prostate cancer, brain injury, primate health, surgery

- *FINANCE-ECONOMICS-BUSINESS*

  Stock market, bank loans, credit decisions, apparel analyses, market segmentation

- *SOCIAL-POLITICAL-ENVIRONMENTAL*

  Socio-ecological interactions, wars, urban water use, rainfall, forest attributes

- *MATH-ENGINEERING*

  Logic circuits, automata dynamics, genetic algorithm & neural network preprocessing, chip manufacturing, pattern recognition, decision analysis

- *OTHER*

  Textual analysis, language analysis

What RA is

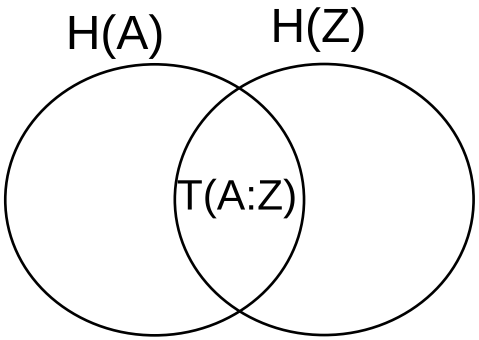
- Reconstructability Analysis (RA) = Information theory + Graph theory, a probabilistic graphical modeling technique
- Model = structure applied to data
- RA structure = hypergraph (relations not only pairwise)
- RA model = a (joint or conditional) probability distribution simpler (fewer df) than the data, capturing much of the information in the data

Two types of RA explorations

- ***Neutral search*** (clustering): find relations among all variables
- ***Directed search*** (classification): predict DVs from IVs. Want:
  - High accuracy (information captured) (low error) measured by
    - %ΔH = % reduction of uncertainty *(like variance)*
    - %c = % correct in prediction *(a general measure)*
  - High model simplicity (low complexity) = low Δdf
  - Model selection criteria trade off these two objectives

Uncertainty reduction: the primary measure

- Reduction of uncertainty (Shannon entropy), a simple example



	Z_0	Z_1	
A_0	.67*.5	.33*.5	.5
A_1	.33*.5	.67*.5	.5
df=3	.5	.5	

- $p(Z_1)/p(Z_0)=$ 1:1, not knowing A $\rightarrow$ 2:1 or 1:2, knowing A

- $\Delta H(Z) = T(A:Z) / H(Z) = 8\%$

- 8% reduction in uncertainty (here) is *large* (unlike variance!)

Model selection criteria

Tradeoff between accuracy & simplicity (error & complexity)

- *Conservative:* Bayesian Information Criterion (BIC)
- *Aggressive:* Akaike Information Criterion (AIC)

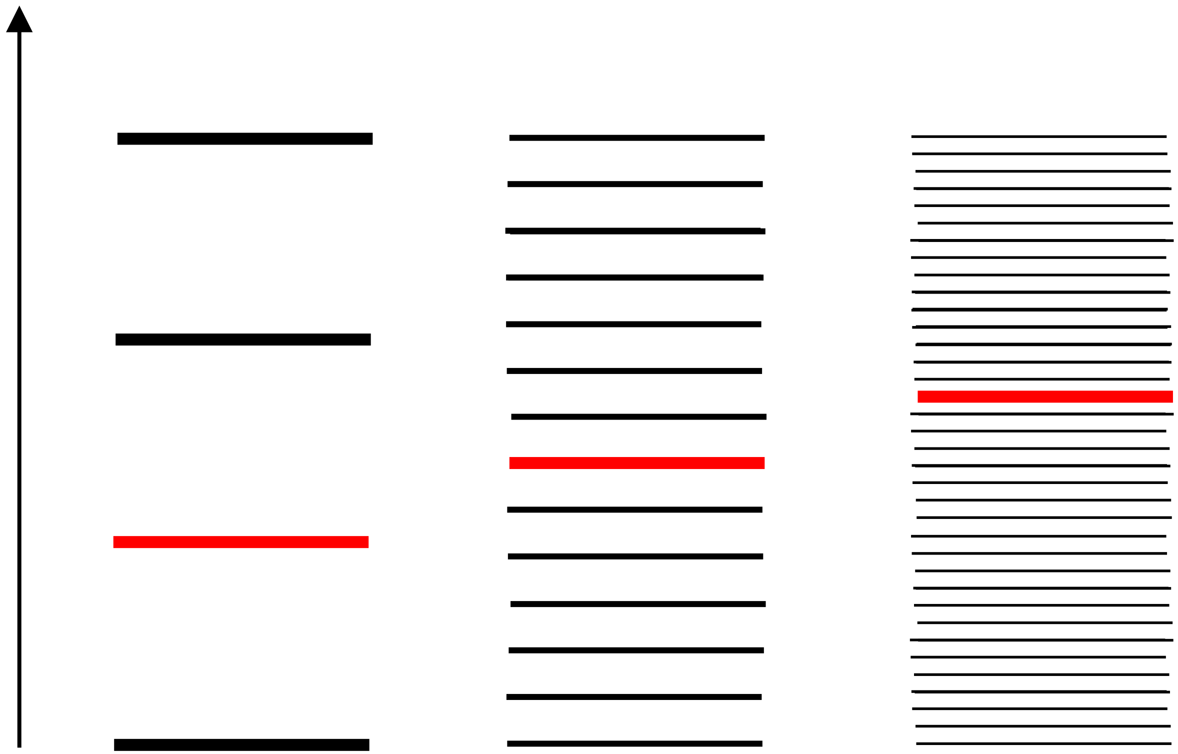
  Incremental p-value (IncrP)

- AIC & BIC: linear combinations of error & complexity; BIC penalizes more for complexity: weights it by ln(N)
- IncrP uses Chi-square p-values to pick models whose difference from -- & every incremental step from -- independence is statistically significant

Degrees of refinement of RA model search

Complexity

(degrees of freedom)



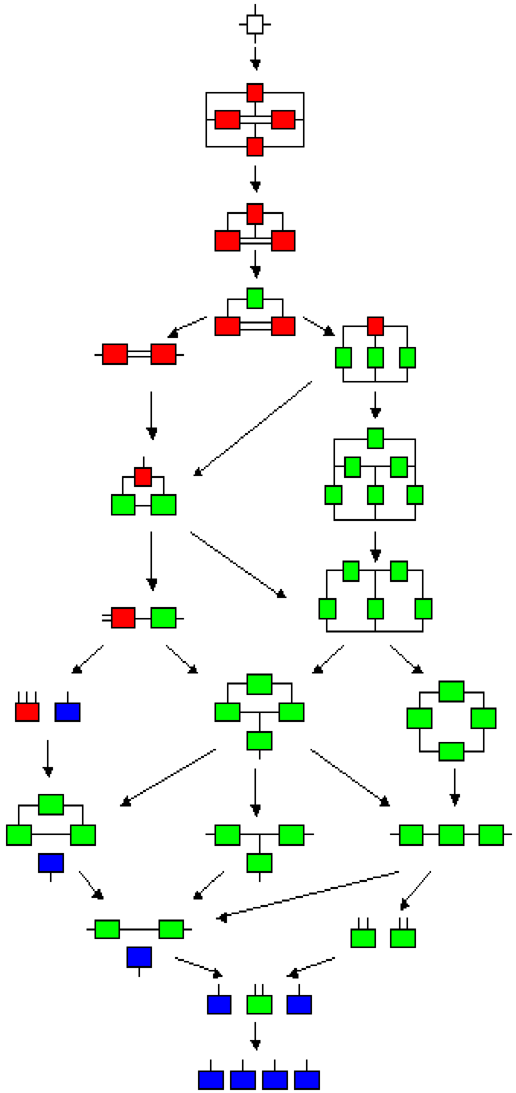
Variable-based

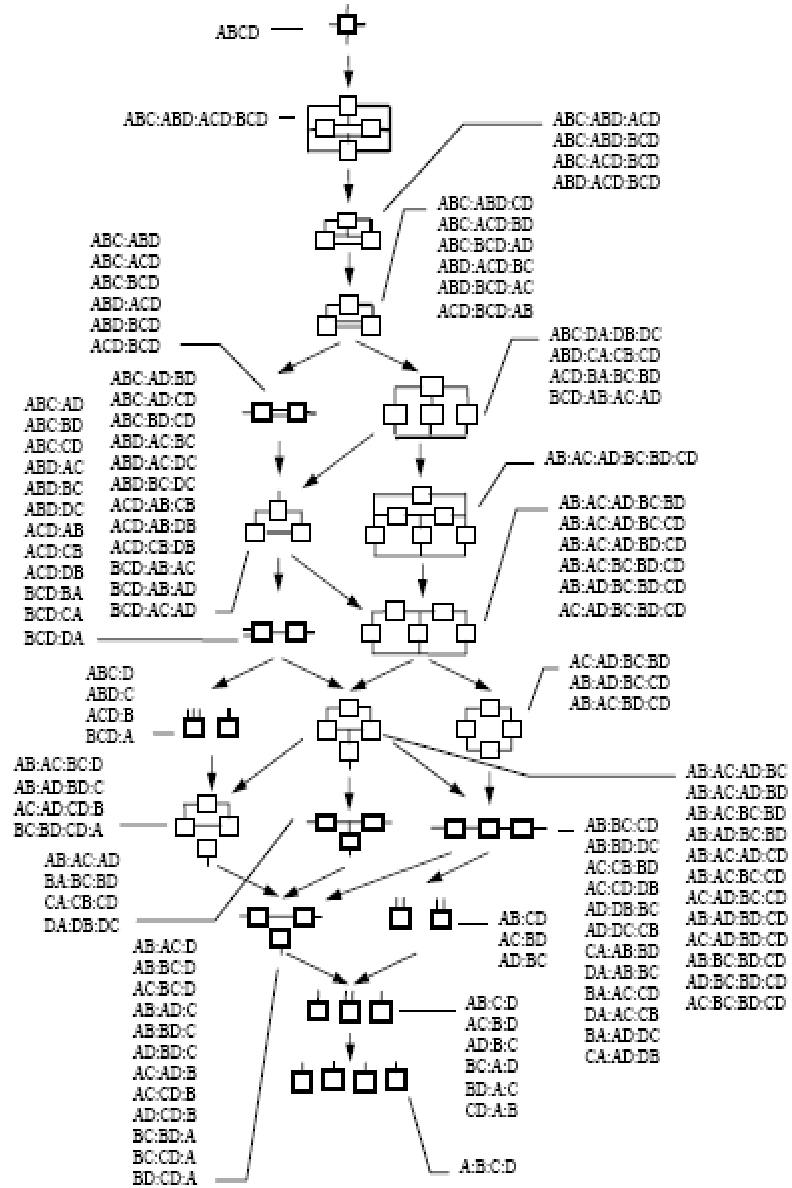
No **loops**
COARSE

With **loops**
FINE

State-based
ULTRA-FINE

4 variables, neutral systems: 114 models





Combinatorial explosion of possible structures

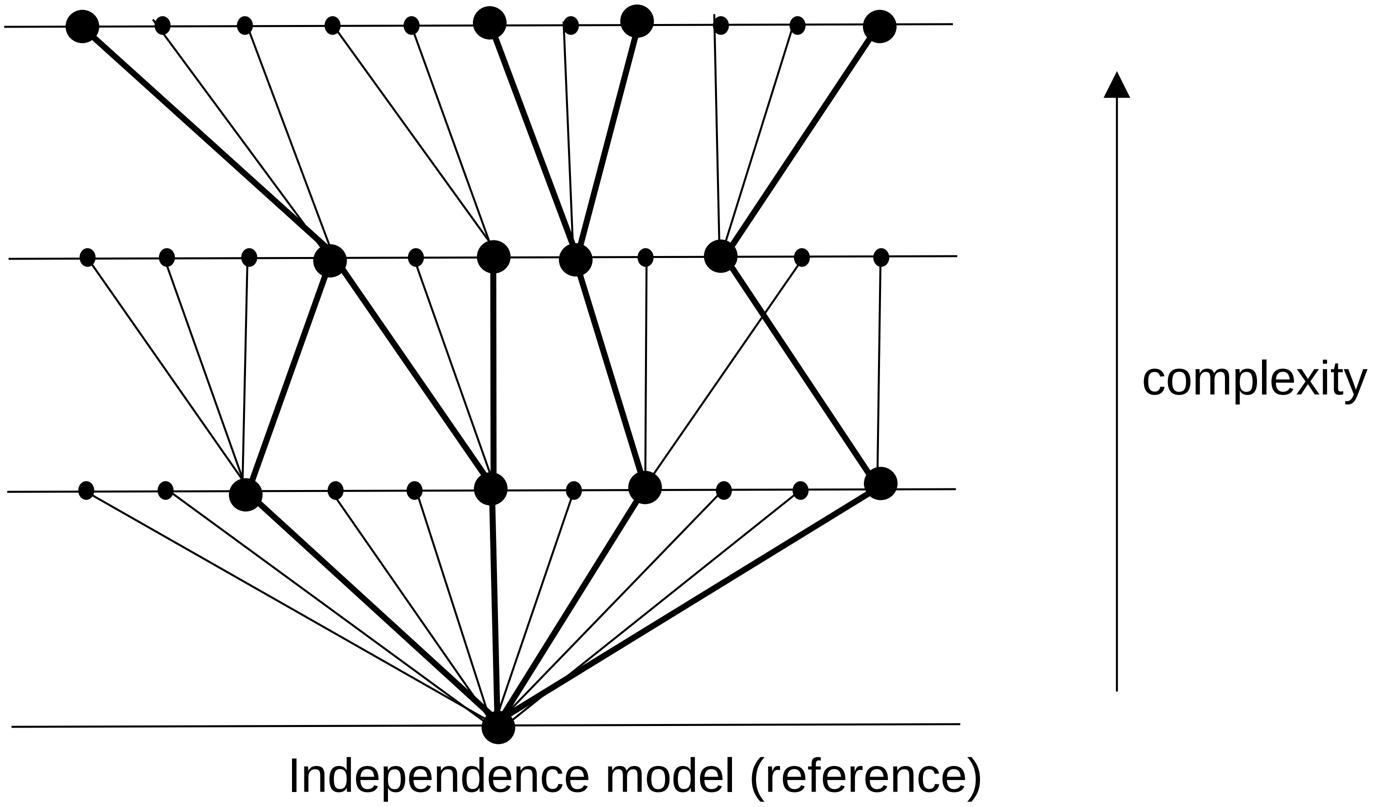
# variables	**2**	**3**	**4**	**5**	**6**	**7**
7# neutral VB models (loops)	2	9	**114**	6,894	7,785,062	2.4 10^{12}
For 1 DV:						
# directed VB models (loops)	2	5	19	167	7,580	7.8 10^{6}
# directed VB models (no loops)	2	4	8	16	32	64
For binary variables:						
# neutral SB models (loops)	14	*even more severely* exponential				

NEED INTELLIGENT HEURISTICS

TO DO **EXPLORATORY** MODELING **with <u>52</u> variables (Preece data) or <u>560</u> variables (Wright data)**

Can now explore a few 100 variables; if parallelized could deal with more.

Searching the space of possible models



2. Sample results

2.1 **Preece** data: analysis complete

auto accidents

- Neutral *coarse searches*
- Directed *coarse, fine, & ultra-fine searches*

2.2 **Wright** (PROTECT) data: analysis underway

auto/motorcycle/bike accidents, hit pedestrians, falls

- Directed *coarse & fine searches*

Other data sets to follow

2.1 Preece data

- 52 variables
- Variable types
  - P = patient characteristics (17 variables)
  - Y = symptoms (25): subjective reports
  - G = signs (4): objective indicators
  - C = cognitive deficits (5)
  - N = neurologic deficits (1)
- N = 337; reduces to 175 or less if exclude missing data

Occam input file *(partial, Preece)* (note missing data)

preece04slide - Notepad

File Edit Format View Help

```
:action
search

:nominal
#                                       P= patient(16) Y=symptom (25) G=sign (6) N=neurologic (1) C= cognitive (5)
subjectid,1,    0,      id      #1              different format for the 2 studies
study,2,        0,      st      #2              which study the data is from (1)PAH N=55 or(2) RBWH N=282
pinjgrp,5,      1,      pij     #3      p       Injury Group patient or control
page,7,         1,      pag     #4      p       age
psex,2,         1,      psx     #5      p       sex
pyred,6,        1,      pye     #6      p       years if education
pedlevel,8,     1,      ped     #7      p       highest level of education
ypainscale,5,   1,      ypn     #8      y       standard painscale used by hospitals
yemoscale,5,    1,      yem     #9      y       sacle defining emotional state(0 no problems 1 few 2 moderate 3 many problems)
ydassd,5,       1,      ydd     #10     y       Depression Anxiety Stress Scales measure of DEPRESSION(Subjective experience questionnaire)
ydassa,6,       1,      yda     #11     y       Depression Anxiety Stress Scales measure of ANXIETY(Subjective experience questionnaire)
ydasss,4,       1,      yds     #12     y       Depression Anxiety Stress Scales measure of STRESS (Subjective experience questionnaire)
ghrssleep,5,    1,      ghl     #13     g       number of hours of sleep, divided in less than normal normal=8hr and greater than normal
puhrsleep,5,    1,      pul     #14     p       usual number of hours of sleep, divided in less than normal normal=8hr and greater than normal
precentill,3,   1,      pri     #15     p       recent illness 0 no 1 yes
pmedication,3,  1,      pmd     #16     p       current medications 0 no 1 yes
ppainkller,3,   1,      ppk     #17     p       currently on painkillers 0 no 1 yes
ppreheadinj,3,  1,      pph     #18     p       have they had previous head injury 0 no 1 yes
gpreloclgth,7,  1,      gpl     #19     g       how long unconscious
gprecon,3,      1,      gpc     #20     g       previous concussion 0 no 1 yes
pnumprecon,8,   1,      pnp     #21     p       how many previous concussions. N = 16 there were only 7 different values so each code defines a raw value
ggcs,4,         1,      ggc     #22     g       glasgow coma scale a measure of the level of unconsciousness lower score = deeper level of unconsciousness
chazpt,10,      1,      chp     #23     c       hazard perception test measures how quickly potential driving hazards are predicted
pdbqerror,13,   1,      pqe     #24     p       Driver Behavior Questionaire errors self reported driving errors and violations
pdbqviol,14,    1,      pqv     #25     p       Driver Behavior Questionaire violations


:data
# variable number, short name,  number of missing
#1      2       3       4       5       6       7       8       9       10      11      12      13      14      15      16      17      18      19      20      21      22      23      24      25      26
# ID    st      ij      ag      sx      ye      ed      pn      em      dd      da      ds      hl      ul      ri      md      pk      ph      pl      pc      np      gc      hp      qe      qv      xc
# 0     0       1       7       0       87      87      116     119     127     127     127     86      85      83      47      107     137     154     285     285     141     55      161     150     57
1       0       3       1       1       2       3       .       .       .       .       .       0       0       1       0       .       .       .       1       5       1       .       .       .       .
2       0       3       0       0       0       1       .       .       .       .       .       1       0       0       0       .       .       .       1       4       0       .       .       .       .
4       0       3       3       0       2       2       .       .       .       .       .       3       3       0       1       .       .       .       0       0       0       .       .       .       .
7       0       3       0       1       1       2       .       .       .       .       .       1       0       1       1       .       .       .       0       0       0       .       .       .       .
8       0       3       2       0       .       .       .       .       .       .       .       .       .       .       .       .       .       .       .       .       0       .       .       .       .
9       0       3       1       1       3       5       .       .       .       .       .       2       2       0       1       .       .       .       1       2       0       .       .       .       .
11      0       2       3       1       0       0       .       .       .       .       .       2       0       1       1       .       .       .       0       0       2       .       .       .       .
13      0       3       2       1       4       6       .       .       .       .       .       1       0       0       0       .       .       .       0       0       0       .       .       .       .
15      0       2       3       1       0       3       .       .       .       .       .       0       0       1       1       .       .       .       1       6       2       .       .       .       .
16      0       3       1       1       1       1       .       .       .       .       .       1       2       0       1       .       .       .       0       0       .       .       .       .       .
17      0       0       0       1       2       4       .       .       .       .       .       0       0       1       0       .       .       .       0       0       .       .       .       .       .
18      0       0       0       1       3       2       .       .       .       .       .       0       1       0       0       .       .       .       1       3       .       .       .       .       .
19      0       0       1       1       4       5       .       .       .       .       .       1       0       0       0       .       .       .       0       0       .       .       .       .       .
20      0       0       0       1       3       4       .       .       .       .       .       0       0       0       0       .       .       .       0       0       .       .       .       .       .
21      0       0       0       1       3       5       .       .       .       .       .       0       0       0       0       .       .       .       1       1       .       .       .       .       .
22      0       0       0       1       3       6       .       .       .       .       .       0       0       0       0       .       .       .       0       0       .       .       .       .       .
23      0       0       3       1       4       5       .       .       .       .       .       0       0       0       0       .       .       .       1       1       .       .       .       .       .
24      0       0       0       1       1       2       .       .       .       .       .       0       1       1       1       .       .       .       1       1       .       .       .       .       .
26      0       2       1       1       0       1       .       .       .       .       .       2       0       0       1       .       .       .       0       0       2       .       .       .       .
27      0       0       1       0       3       5       .       .       .       .       .       0       0       1       0       .       .       .       0       0       .       .       .       .       .
28      0       2       0       1       0       1       .       .       .       .       .       .       .       .       .       .       .       .       .       .       2       .       .       .       .
29      0       3       4       1       3       5       .       .       .       .       .       1       0       0       0       .       .       .       0       0       0       .       .       .       .
30      0       3       3       1       0       3       .       .       .       .       .       0       2       1       1       .       .       .       0       0       1       .       .       .       .
3
```

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1/19/2015

Neutral coarse search results

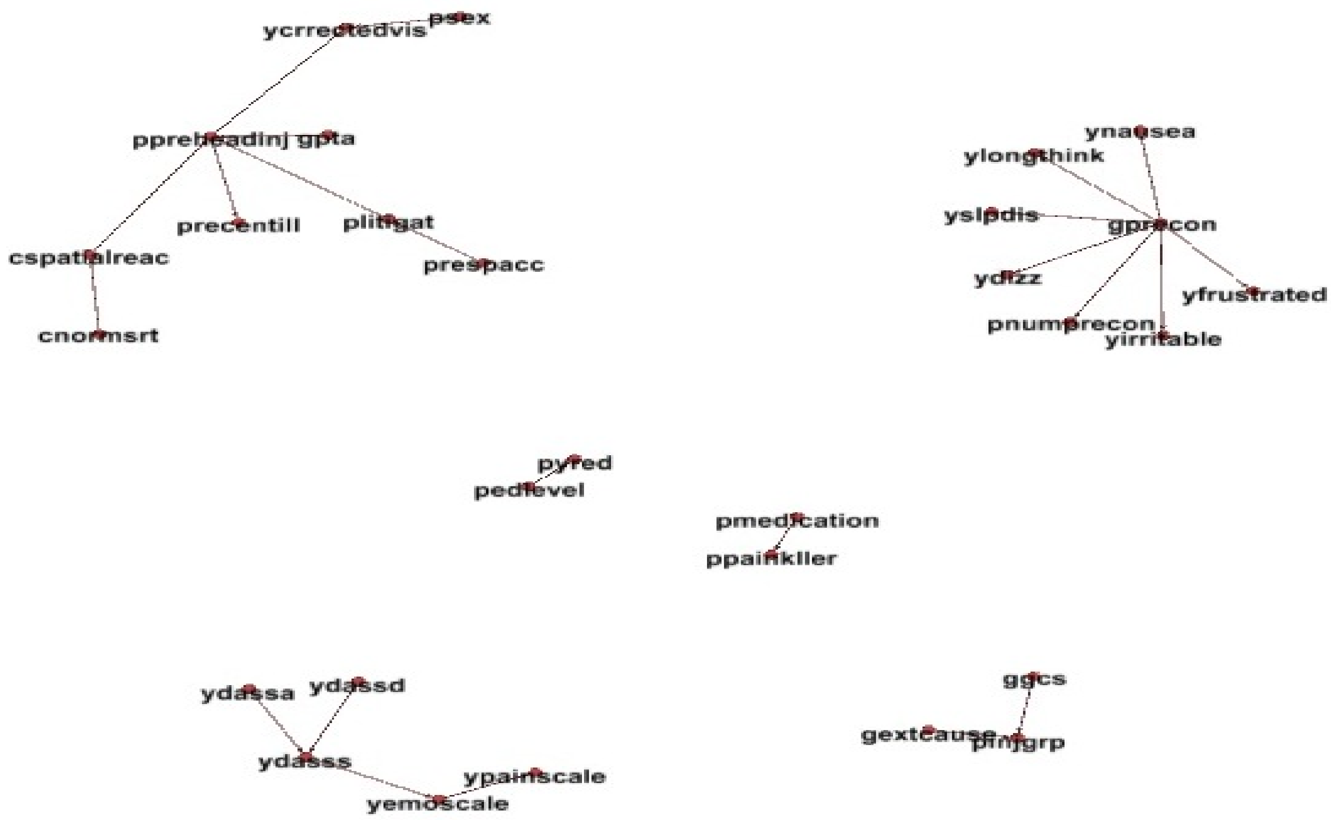
- A neutral search model is a set of associations (relations)
- Variables here with original (high) cardinalities & missing data

- Best BIC (conservative) model has:

51 components: red: $p < .05$; purple: $.05 < p < .1$; **C, N variables in bold**
PijGpc:PijGgc:PijGxc:Pag:PsxYcv:PyePed:PyePri:YpnYem:YemYds:YddYds:
YdaYds:YdsPph:GhlPri:PulPri:PriPph:**PriCdg:PriNlr**:PmdPpkGpc:PpkPph:PphGpl:
PphPqe:PphPqv:PphPlg:**PphCsr**:PphYcv:PphPiq:PphGpt:GpcPnp:**GpcChp:GpcCsc:**
GpcYhs:GpcYdz:GpcYna:GpcYns:GpcYsd:GpcYfa:GpcYir:GpcYdp:GpcYax:GpcYfr:
GpcYfg:GpcYcn:GpcYtk:GpcYbr:GpcYls:GpcYdv:GpcYrs:GpcYaz:GpcYrm:PlgPac:
CnrCsr

Neutral coarse search network

- Association network = hypergraph (but below is a graph)
- 23 **p ≤ 0.1** (15 **p ≤ 0.05**) associations in BIC model



Neutral coarse search associations

- Predictive success (%ΔH, Δ%c relative to independence) (p ≤ 0.05)

v1	v2	%ΔH(2|1)	%ΔH(1|2)	p-value	N	Δ%c(2|1)	Δ%c(1|2)	v1	v2
Ggc	Pij	34.5	86.5	0.000	196	9.7	7.7	glasgow coma scale	Injury patient/control
Gxc	Pij	32.9	12.6	0.000	280	20.4	14.3	external cause	Injury patient/control
Ped	Pye	41.3	34.8	0.000	248	32.3	27.4	highest educ level	years of education
Yem	Ypn	6.4	6.1	0.000	218	5.0	2.3	emotional problems	painscale
Yds	Yem	6.0	27.8	0.000	210	3.8	0.0	stress	emotional problems
Ydd	Yds	43.6	26.0	0.000	210	1.4	1.9	depression	stress
Yda	Yds	54.7	32.6	0.000	210	0.0	2.9	anxiety	stress
Pmd	Ppk	50.7	57.6	0.000	230	28.3	15.7	current medications	painkillers
Gpc	Pnp	57.0	100.0	0.000	52	11.5	30.8	previous concussion	# previous concussion
Pac	Plg	26.5	12.3	0.000	201	0.0	12.4	caused accident	case litigated
Cnr	Csr	48.6	48.3	0.000	210	34.3	31.0	reaction time norm	reaction time
Psx	Ycv	6.5	8.8	0.000	197	2.0	0.0	sex	corrected vision
Gpc	**Ydz**	**13.7**	**21.9**	**0.003**	**52**	**0**	**9.6**	**previous concussion**	**dizzy**
Csr	Pph	5.3	2.3	0.010	187	5.3	4.8	reaction time	previous head injury
Gpc	**Yfr**	**9.1**	**17.3**	**0.011**	**52**	**1.9**	**9.6**	**previous concussion**	**frustrated**

Directed searches

- DVs (cognitive, neurological deficit variables)
- #bins excludes missing values

	#bins		N	
cdgtcorrect	6	Cdg	255	**Digit Symbol Substitution neuropsychological test**
cnormsrt	6	**Cnr**	210	**Spatial Reaction Time normalized for age and sex**
cspatialreac	6	csr	214	Spatial Reaction Time test: how quickly patient responds to visual stimuli
nlogmar	3	Nlr	209	**LogMAR Log of Minimum Angle of Resolution (visual acuity)**

Cnr coarse, fine, ultra-fine searches

Predict Cnr: reaction time, normalized by age, sex (rebin |Cnr| = 2: ~ 50-50)

MODEL	Δdf	p	%ΔH	%c		N=175		
COARSE, single component predictors								
Cdg Gpt Cnr	3	0.00	10.6	64.6	**BIC, AIC**	***Cdg = digit symbol test***		
Pph Cdg Gpt Cnr	7	0.00	13.1	66.9	**IncrP**	***Gpt = amnesia***		
Cnr (independence=reference)	0	1.00	0.0	***50.9***		***Pph = previous head injury***		
FINE								
Cdg Cnr : Gpt Cnr	2	0.00	8.8	64.6	**BIC**			
Pri Cnr : Pph Cnr : Cdg Gpt Cnr	6	0.00	14.7	70.3	**AIC**	*Pri = recent illness*		
Pye Cnr : Pph Cnr : Cdg Gpt Cnr	5	0.00	12.9	67.4	**IncrP**	*Pye = years education*		
ULTRA-FINE (state-based model)								
Pph_1 Cdg_1 Cnr : Cdg_0 Gpt_1 Cnr	2	0.00	12.4	64.8	**BIC**			
Cnr (independence=reference)	0	1.00	0.0	***50.9***				

Cnr ultra-fine model

Model: $Pph_1\ Cdg_1\ _{Cnr} : Cdg_0\ Gpt_1\ _{Cnr}$

Odds (high is good) = Cnr_0/Cnr_1(model) = p(fast = normal reaction)/p(slow)

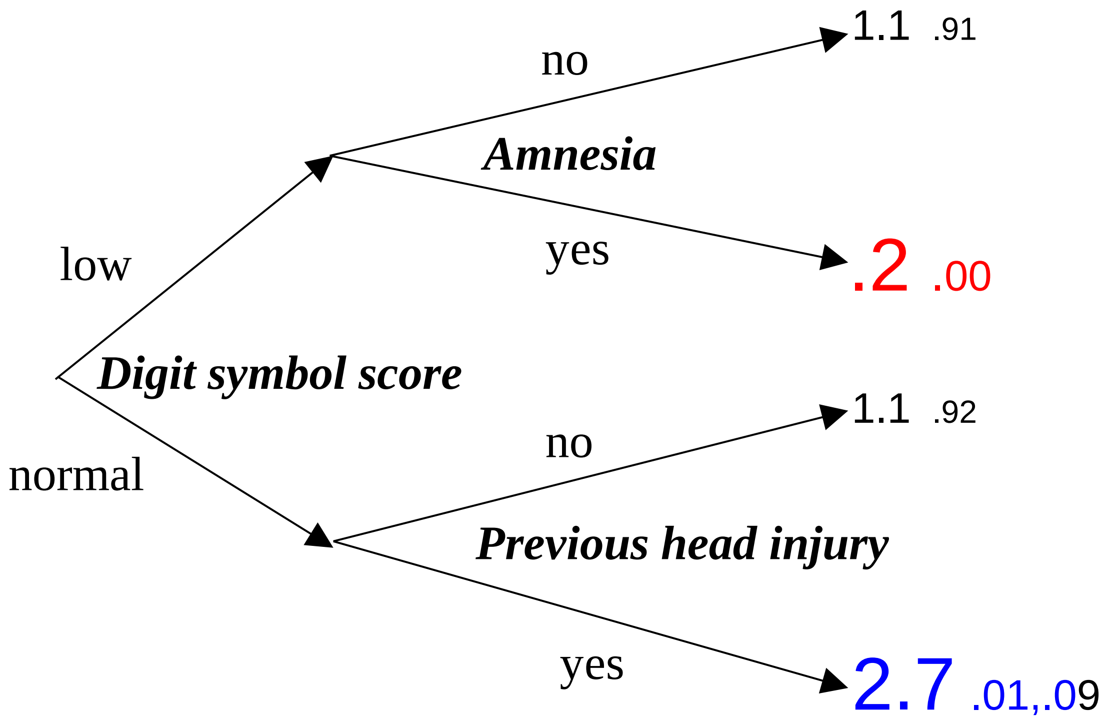
Pph_1 previous head injury, Cdg_1 high digit score; Gpt_1 amnesia

IV states				conditional probabilities of DV					
				data		model			
Pph	Cdg	Gpt	N	Cnr_0	Cnr_1	Cnr_0	Cnr_1	Odds	p
0	0	0	20	0.40	0.60	0.52	0.48	1.1	.92
0	0	**1**	19	0.16	0.84	0.16	0.84	0.2	.00
1	0	0	30	0.57	0.43	0.52	0.48	1.1	.90
1	0	**1**	18	0.17	0.83	0.16	0.84	0.2	.00
0	1	0	24	0.50	0.50	0.52	0.48	1.1	.91
0	1	1	13	0.61	0.39	0.52	0.48	1.1	.93
1	1	0	38	0.76	0.23	0.73	0.27	2.7	.01
1	1	1	14	0.64	0.36	0.73	0.27	2.7	.09
			176	0.51	0.49	0.51	0.49	1.0	

Cnr decision tree from conditional probabilities

Reaction time **Odds** (probability fast/ probability slow)

& p-values relative to marginal prob. (odds = 1)



Cnr decision tree, verbally

- For low performance on digit symbol test, amnesia predicts slow reaction time.
- For normal performance on digit symbol test, previous head injury *increases* the probability of fast (normal) reaction time. THIS IS *ANOMALOUS*.
  - Need to see if it would be replicated in another data set.
  - Possible explanation: prior exposure to Reaction Time test introduces a practice effect.
  - If Reaction Time is so vulnerable to a practice effect that it no longer discriminates concussed from non-concussed, then it’s probably not an appropriate measure for this purpose.

2.2 Wright (PROTECT) data

- 560 variables (302 variables within 1st two weeks)
- Variable types
  - A = admin (32 variables) #1-32
  - P = patient characteristics (134 variables) #405-538
  - Y = symptoms (8 variables): subjective reports #551-558
  - G = signs (13 variables): objective indicators #539-550, 560
  - C = cognitive deficits (6 variables) #33-38
  - N = neurologic deficits (367 variables) #39-404, 559
- N = 882 patients

Directed searches

- DVs = deficit variables

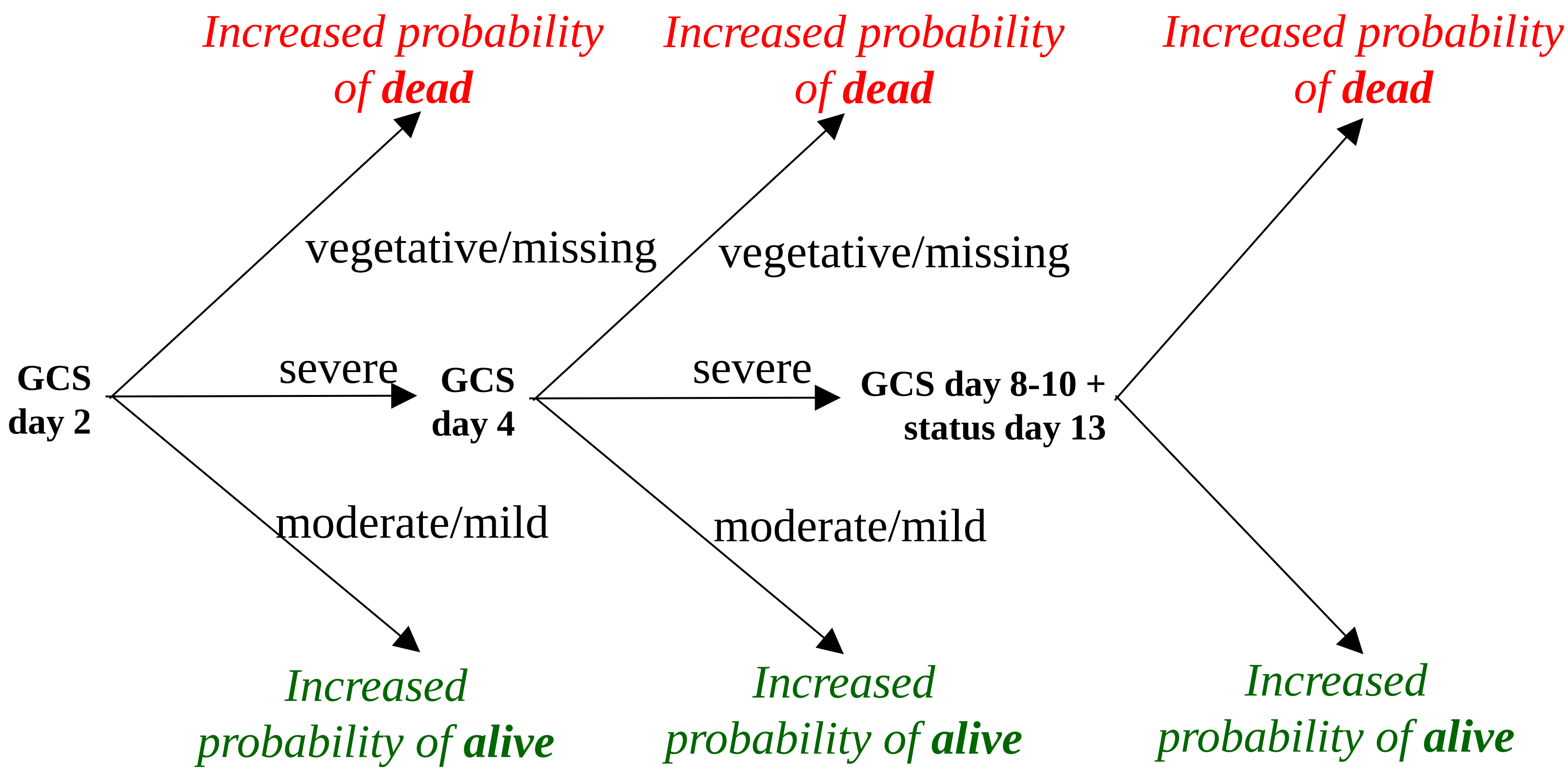
	#bins		N		# IVs
mort2	2	**Gvn**	764	**Mortality at 2 weeks**	302
	0=not dead; 1=dead				
gose	8	Nvm	882	Total extended Glasgow Outcome Scale	
	1=death; 2=vegetative; 3,4 lower, upper severe disability;				
	5,6 lower, upper moderate disability; 7,8 lower, upper good recovery				

Two lines of current investigation:

1. *Predict mortality at 2 weeks*
2. *Investigate possible progesterone effect*

Predict mortality at 2 weeks

- No surprises: GCS scores, days 2, 4, 9, are best predictors.



Investigate possible progesterone effect

- Earlier studies suggested value of progesterone treatment
- These effects not found in Wright project
- Project is regarded as an exemplar of ‘failed’ studies

- Wright didn’t systematically look for complex effects
- Progesterone *might* have had effect in some *sub*population

- RA detects a *possible* predictive interaction effect
- Likely to be an artifact, but *under investigation*

A possible progesterone effect

- Ngw = sedation (0 no, 1 yes)
- Pup = progesterone treatment (0 no, 1 yes)
- Gvn = status at 2 weeks (0 alive, 1 dead)

IV states			DV cond.prob.		N		
Ngw	Pup	N	Gvn_0	Gvn_1	Gvn_0	Gvn_1	p(margin)
.	0	49	0.41	0.59	20	29	0
0	**0**	190	0.92	**0.08**	175	15	0.01
.	1	49	0.33	0.67	16	33	0
0	**1**	206	0.97	**0.03**	200	6	0
1	**0**	141	0.94	**0.06**	133	8	0
1	**1**	129	0.85	**0.15**	110	19	0.92
		764	0.86	**0.14**	654	110	

- Pup *benefits* if *no* sedation; *harms* if sedation

Effect may be an artifact

- Effect depends on another variable, Nod, being *missing*
- Nod = ‘Was GCS collected in previous 24 hrs’
- Nod missing *N=297*, not missing N=467
- If Nod *not missing*, effect *disappears*
- Value of results depends on *what Nod missing means*
- This is *being explored* with Wright

- *Missing data is frequently a confounder*
- *Analysis always depends on quality of the data*

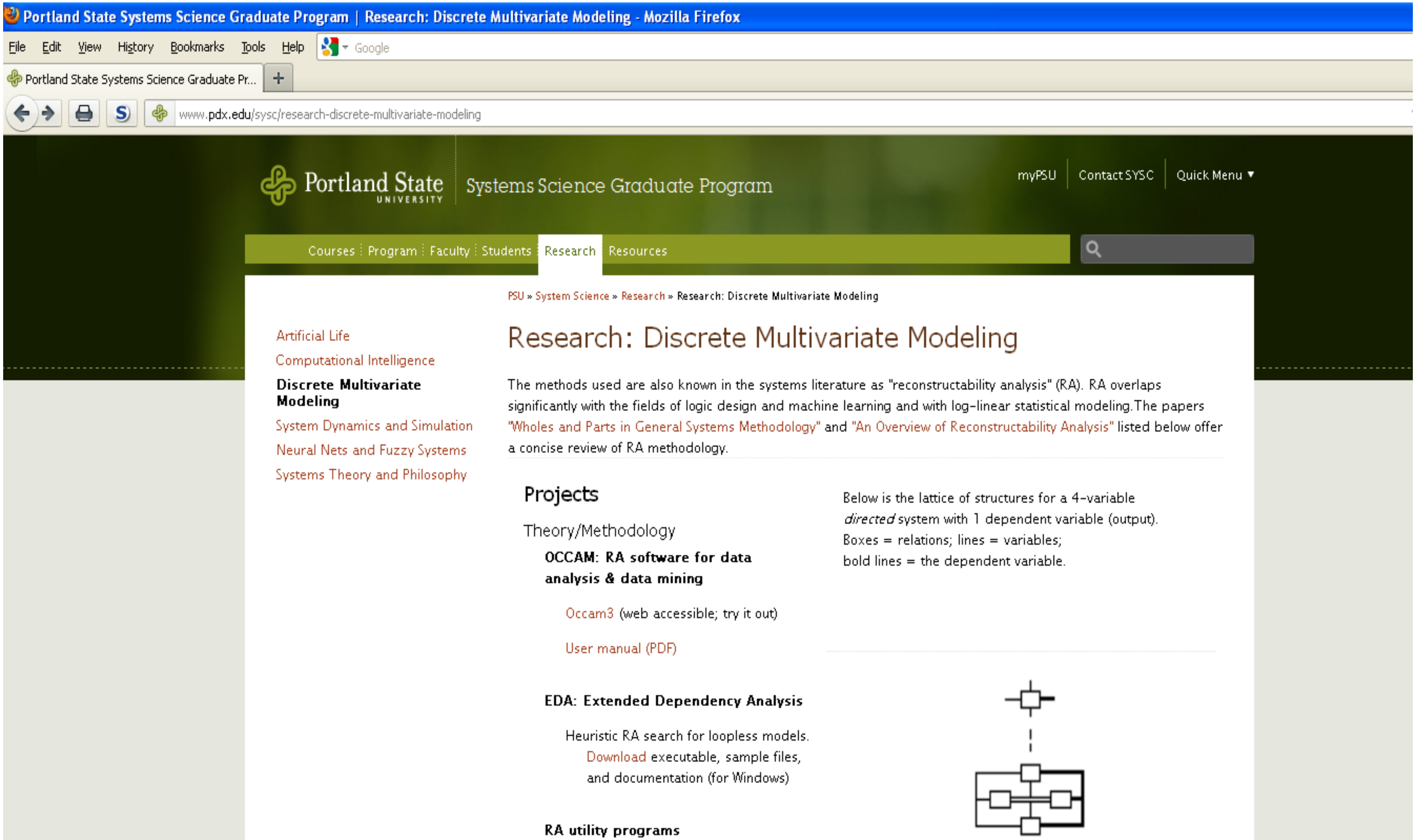
Summary

- Preece data a test bed for analysis protocol. Analysis complete, being written up.
- As an exploratory study, results are tentative, needing *confirmation* on other data sets.
- Wright analysis underway
- These studies are driving *methodological RA innovations.*
- Hope for *additional* data sets (accident, military, sports), with *higher* N, *fewer* missing data, *new* variable types (imaging, genomic, proteomic).
- Work is collaborative with investigators who share data.

RA (DMM) web page

http://pdx.edu/sysc/research-discrete-multivariate-modeling

zwick@pdx.edu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Systems Theory and Philosophy

Research: Discrete Multivariate Modeling

The methods used are also known in the systems literature as "reconstructability analysis" (RA). RA overlaps significantly with the fields of logic design and machine learning and with log-linear statistical modeling.The papers "Wholes and Parts in General Systems Methodology" and "An Overview of Reconstructability Analysis" listed below offer a concise review of RA methodology.

Projects

Theory/Methodology

OCCAM: RA software for data analysis & data mining

Occam3 (web accessible; try it out)

User manual (PDF)

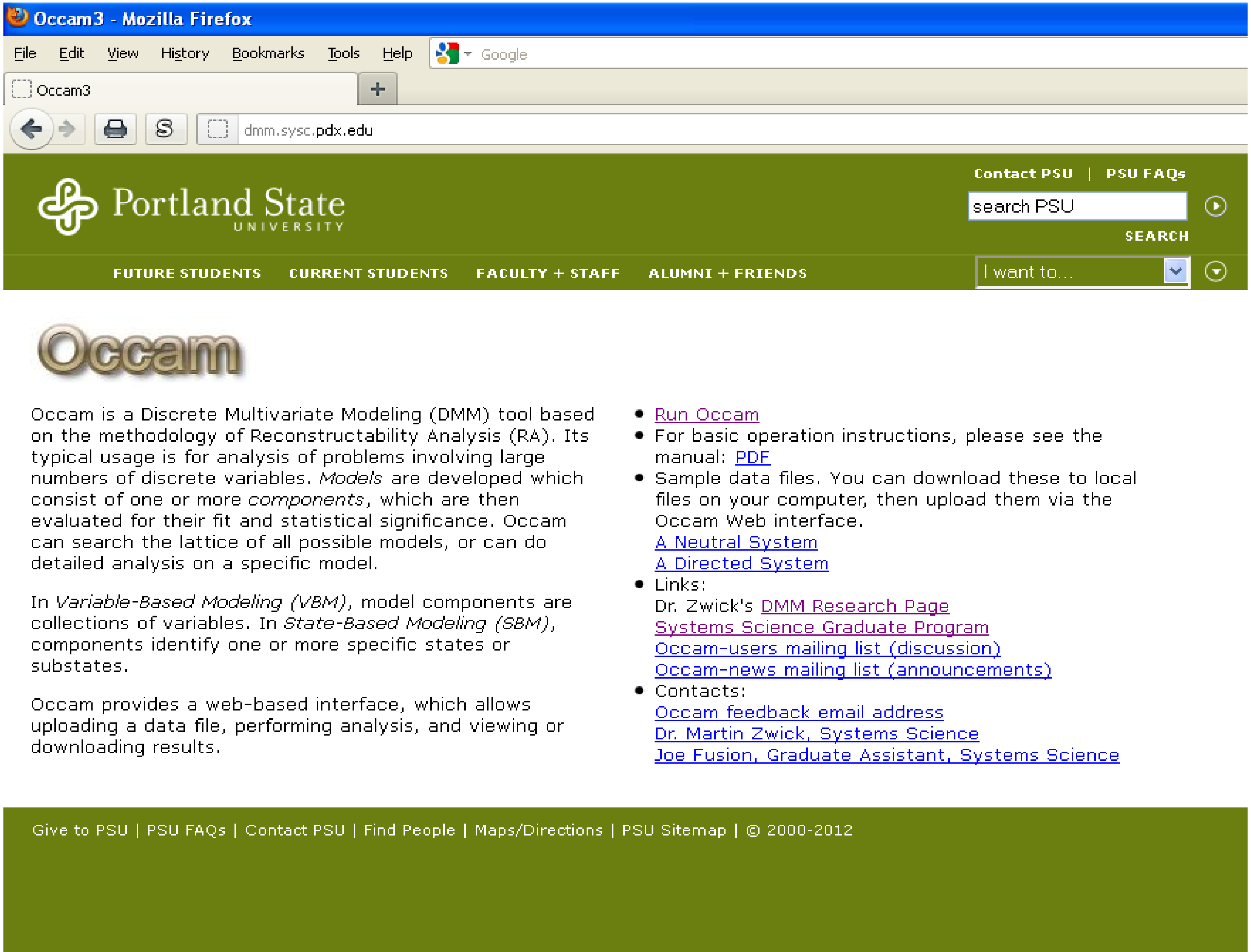
EDA: Extended Dependency Analysis

Heuristic RA search for loopless models. Download executable, sample files, and documentation (for Windows)

RA utility programs

Below is the lattice of structures for a 4-variable *directed* system with 1 dependent variable (output). Boxes = relations; lines = variables; bold lines = the dependent variable.

RA software (Occam)



PSU COURSES

- Discrete Multivariate Modeling (DMM)
  theory course (SySc 551)
  Fall 2016

- Data Mining with Information Theory (DMIT)
  data analysis project course (DMM *not* a prerequisite)
  Winter 2017

THANK YOU