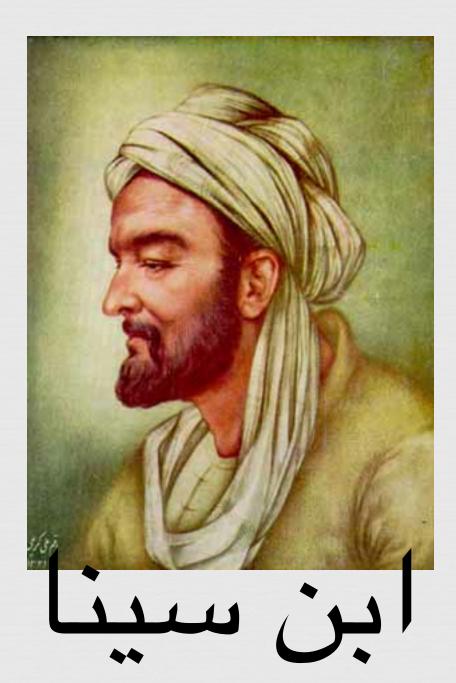
Bud Mishra Prof. of CS, Math, Biology, Genetics & Quant. Bio. Courant, NYU; NYU SoM; MSSM; CSHL, etc.

Causarum Cognitio



#### Abu Ali al-Husayn ibn Abd Allah ibn Sina (ابن سينا) Avicenna (980-1037)



- Commonly known as Ibn Sīnā, or by his Latinized name Avicenna, was a Persian polymath.
- In particular, 150 of his surviving works concentrate on philosophy and 40 of them concentrate on medicine.



Note: A state of the state of the end of the first millennium...
Note: A state of the first and the state of the state of the first and the state of t

- Brought systematic
   experimentation and
   quantification into the
   study of physiology,
- Discovered and elucidated the contagious nature of infectious disease and

#### <u>A Inductive logic and</u> <u>computation...</u>

ᢙ Foundational framework for

- Model checking in computer science,
   A science in the science in the science is a science in the science
- Machine learning and inductive reasoning in artificial intelligence and
- *∽ Causality theory in philosophy*.



# Causality

#### **Reproblematic:**

- Sources of many paradoxes: E.g., Goodman's Grue Paradox.
- CS Regularity: Statistical Inference.
- Computational Complexity.
- Ray Ibn Sina (Avicenna), Al Ghazali, Ibn Rushd (Averroes),
- Pietro Pomponazzi, Giordano Bruno, Niccolo Machavelli, Galileo Galilei (chronological vs. causal effects), Francis Bacon, John Stuart Mill (Mill's Method), <u>David Hume (Regularity)</u>,
- <u>Robert Koch (4 postulates), J.L. Mackie (INUS condition), David Lewis</u> (Counter-factuals), Hans Reichenbach (D-Separation),



### David Hume



Starting point for all contemporary theories of Causation
 Empirical, descriptive inquiry
 To replace unintelligible theoretical explanations

### David Hume

- *Contiguity in time and place* is therefore a requisite circumstance to the operation of all causes. 'Tis evident likewise, that the motion, which was the cause, is prior to the motion, which was the effect.
- *Priority in time,* is therefore another requisite circumstance in every cause. But this is not all. Let us try any other balls of the same kind in a like situation, and we shall always find, that the impulse of one produces motion in the other.
- "Here, therefore is a third circumstance, viz. that of a *constant conjunction* betwixt the cause and effect. Every object like the cause, produces always some object like the effect.
- *CR* "Beyond these three circumstances of contiguity, priority, and constant conjunction, I can discover nothing in this cause..."

#### Probabilistic Causality: Suppes

Causes are *temporally prior* to their effects.
Causes *raise probability* of their effects.
Relationships are between events.
C is a *prima facie cause* of E if it is earlier than *E* and *P*(*E* | *C*) > *P*(*E*).



*C*, a prima facie cause of *E*, is a *spurious cause* of *E* if there is an *S*, earlier than *C* s.t.: *P*(*E* | *C* & *S*)=*P*(*E* | *S*), and *P*(*E* | *C* & *S*) ≥ *P*(*E* | *C*) *A* non-spurious prima facie cause is a *genuine cause*

#### **PCTL Formulas**

Atomic propositions a in A
Atomic propositions a in A
Boolean connectives (¬,^)
State formulas:
State formulas:
State propositions  $\neg f, f^{\wedge}g$   $(fh)_{\geq p}$  and  $[h]_{>p}, 0 \leq p \leq 1$ Path formulas:  $(f U^{\leq t}g, f W^{\leq t}g, where t is non-negative or infinity)$ 

(\*) f and g are state formulas, h is a path formula

#### Derived Operator: "Leads to"

 $f_1 \rightsquigarrow \stackrel{\leq t}{\geq_p} f_2 \equiv AG[(f_1 \to F_{\geq_p} \stackrel{\leq t}{\leq_p} f_2)]$ 

**R**"for all paths, at every state, if  $f_1$  then eventually  $f_2$  within t time units with probability at least p''

Solution Means that there can be any number of transitions between  $f_1$  and  $f_2$ .

**G** Transitions must happen within *t* time units.

#### Types of causes: Summary

Prima facie

- Positively associated with effect
- *G* TP (Temporal Priority Condition) + PR (Probability Raising Condition)

**R** Spurious

- Solution No (or little) influence on effect
- Other causes account better for the effect

**Genuine** 

Son-spurious prima facie causes

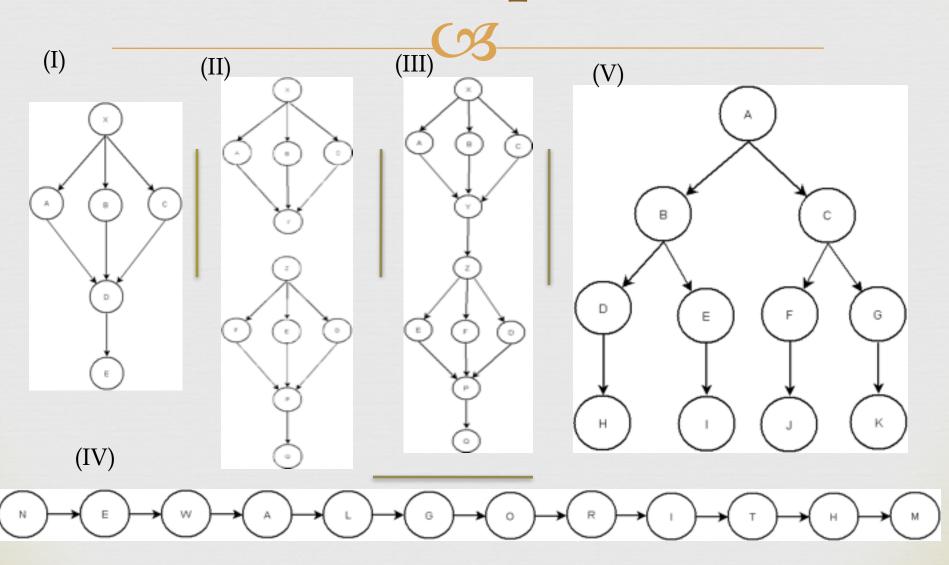
- Solution Next, define these in terms of PCTL
- Use Model Checking to find Prima Facie Causes
- **Use Empirical Bayes Methods** to Classify causes.

## Examples From Neuro S.

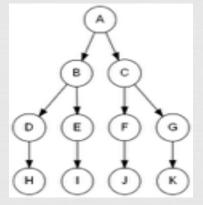
Synthetic MEA data

- Set of 26 neurons, 100,000 firings
- 5 embedded patterns
- Meuron can fire randomly (with probability according to noise level), or be triggered by cause neuron
- Meurons cause eachother to fire in 20-40 time units (and have a 20 time unit refractory period)

## MEA data patterns



#### Results

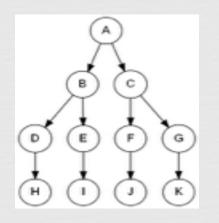


True structure

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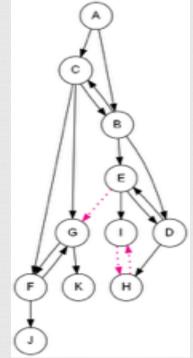
#### Our inference

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Inferred with Granger test

#### Stats

5 patterns, 2 noise levels
For each pattern, 2 runs at each noise level
FDR = # false positives / # total positives
FNR = # false negatives / # all negatives

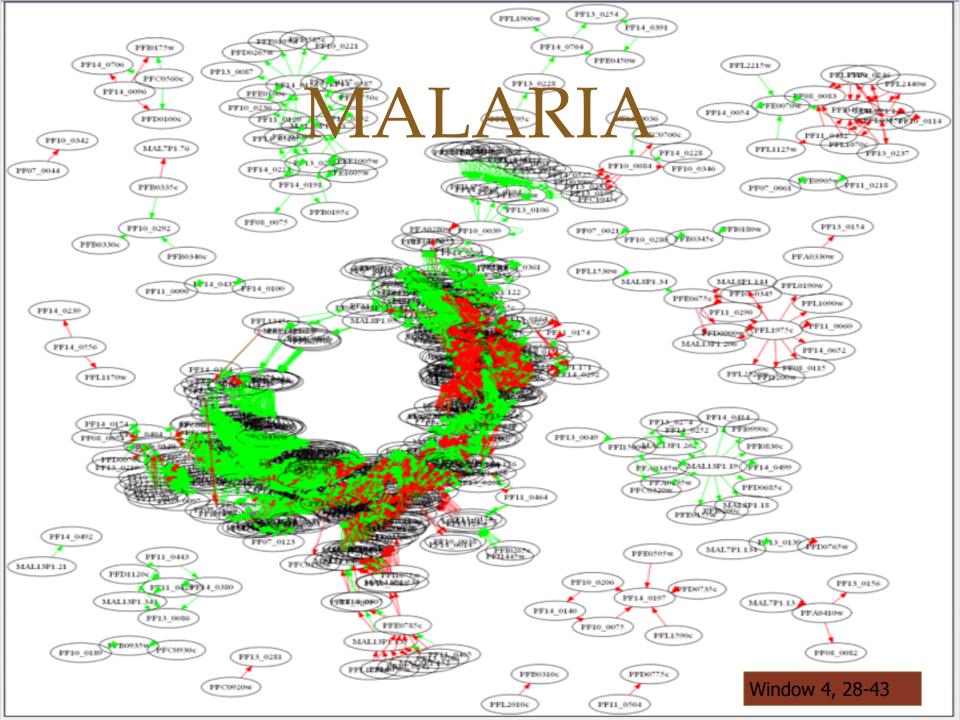
Algorithm	FDR	FNR	Intersection
Temporal Logic	0.0093	0.0005	0.9583
Granger	0.5079	0.0026	0.7530
PC	0.9608	0.0159	0.0671

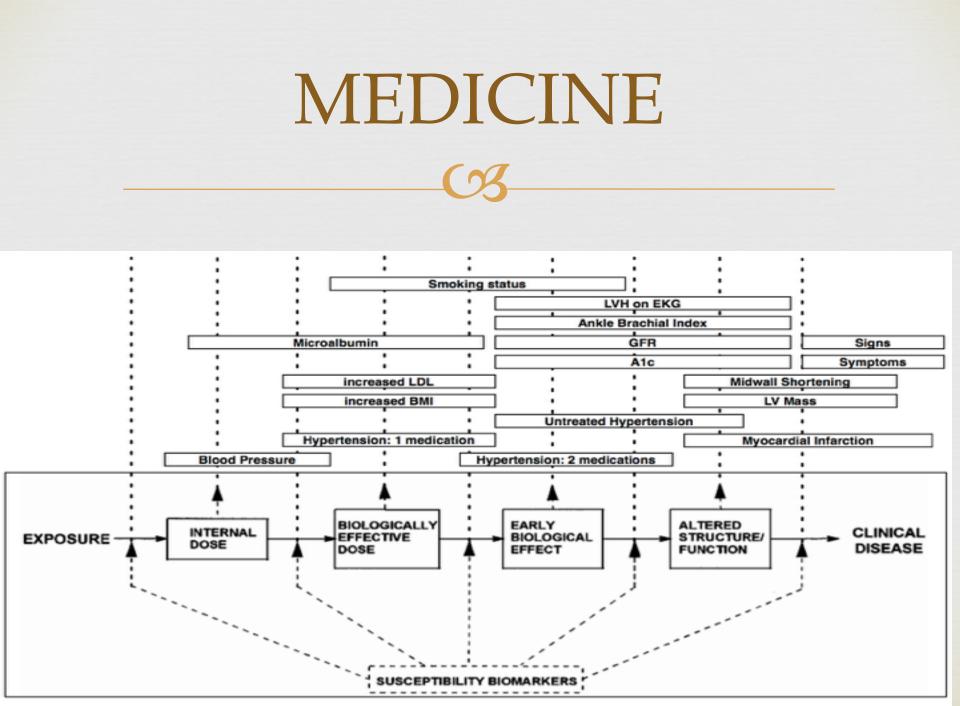
### ANTHRAX

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"source" cluster





# FINANCE

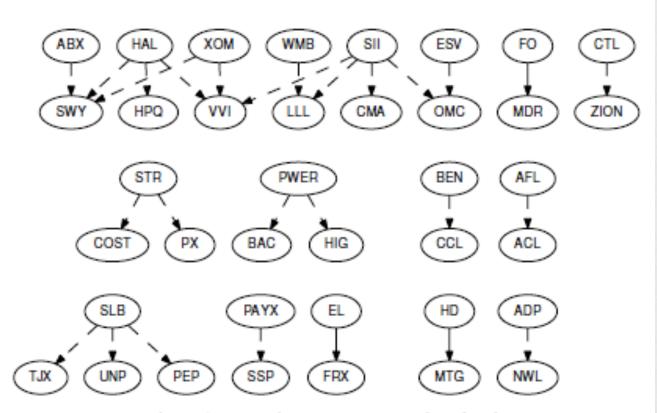
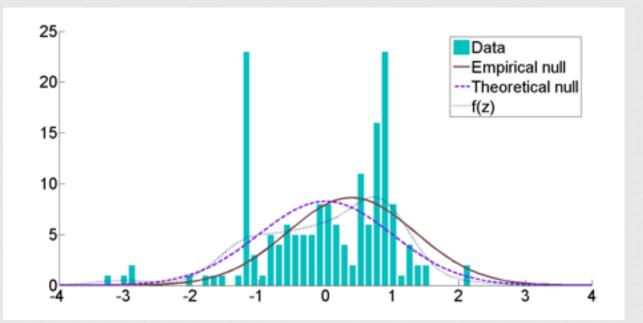


Figure 7.6.: Relationships found in one year of actual market data.

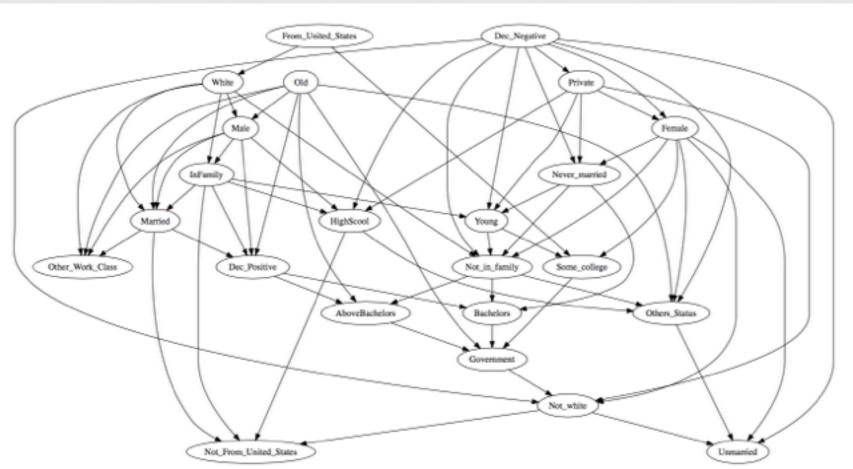
#### POLITICS

- $\bigcirc$  No genuine causes with z>0...
- - G For example "had President Bush NOT said homes, his rating would have gone down"



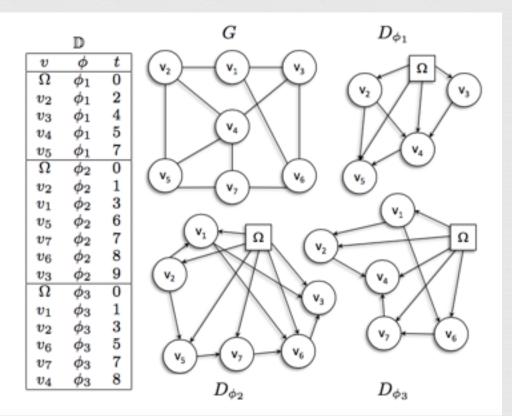
#### Discrimnation

**German Credit Rating** 



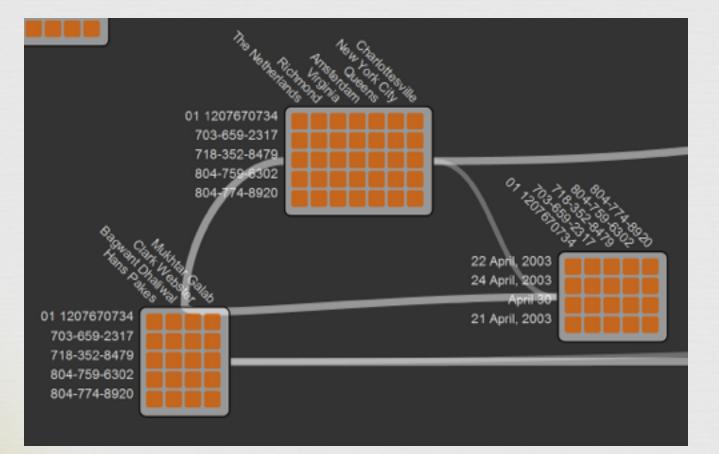
#### Social Influence

(%



24

#### SECURITY



In this case the analyst decided to start with this story of node linking a set of 5 phone numbers to names, locations and date.

It turns out that this odd group is central to communication and coordination between the cells and serves as an efficient starting point for analysis. 25

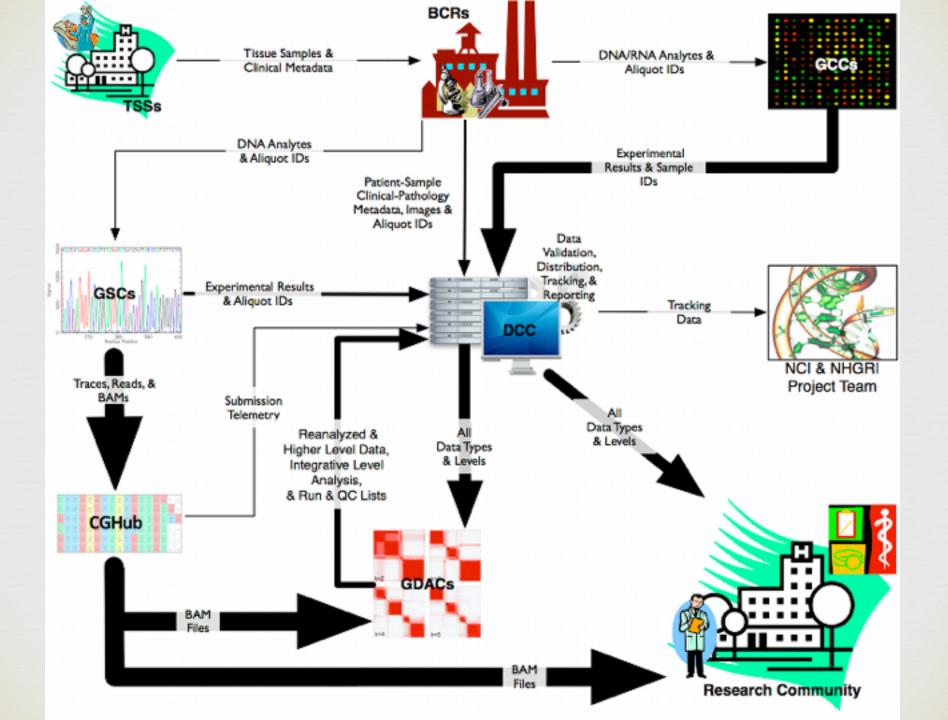
#### CULTUROMICS

(2

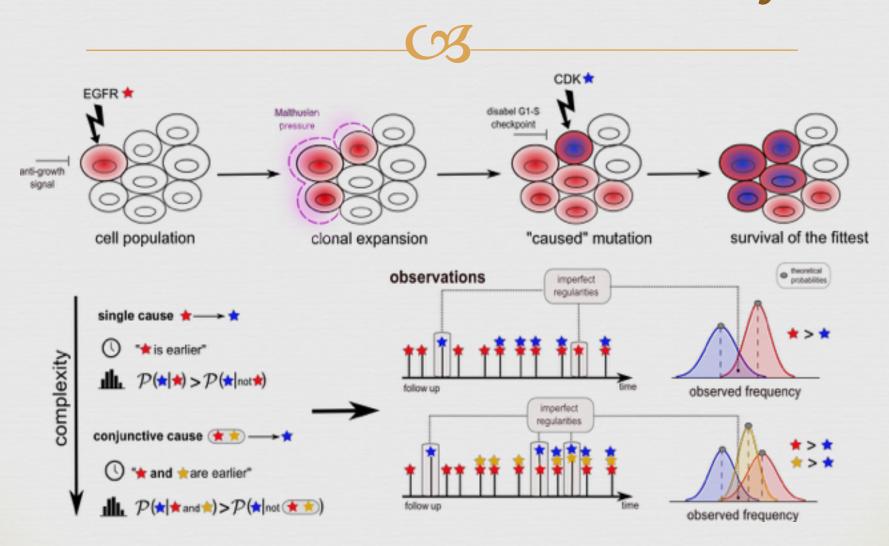
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# Cancer, Causality and Complexity

Patient data without explicit time information

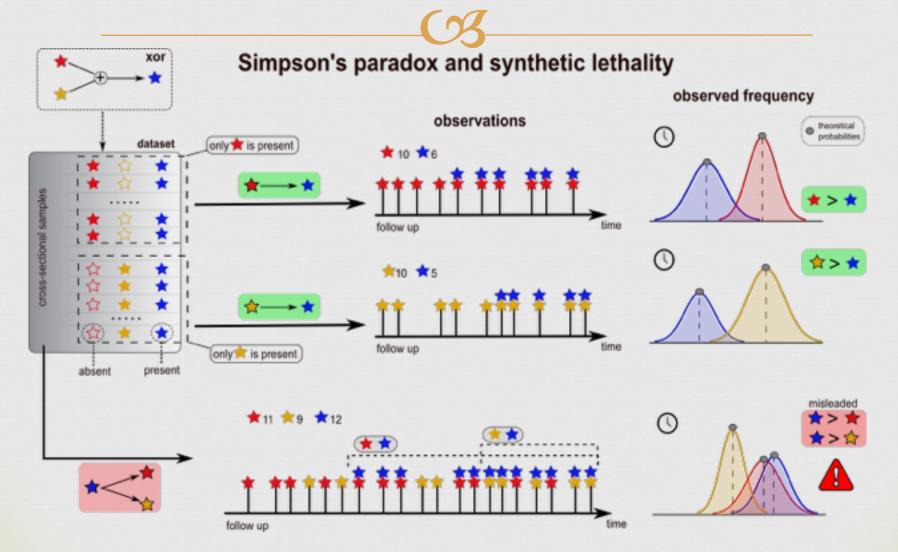


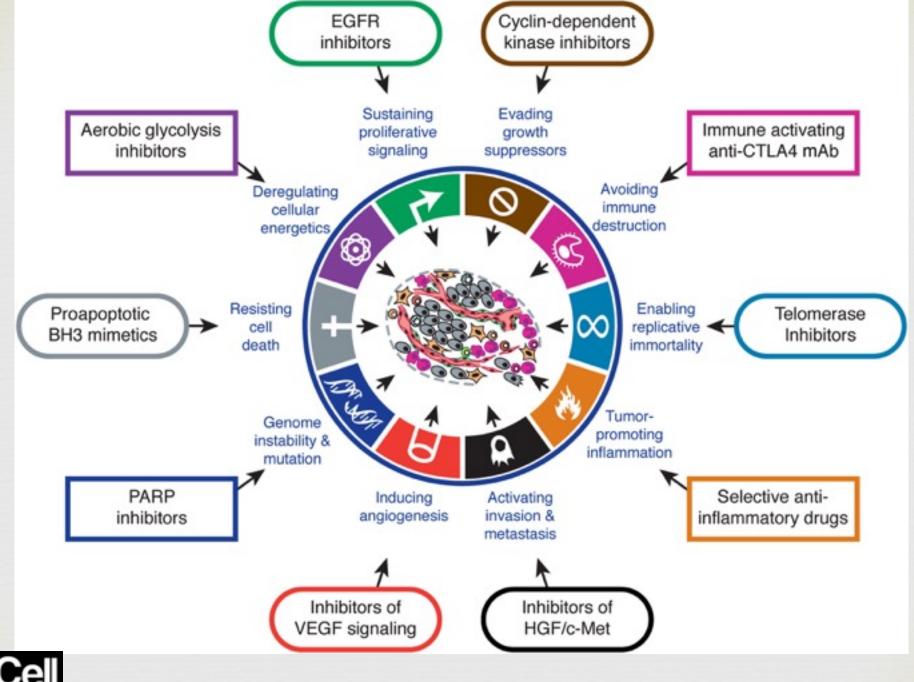
#### **Evolution & Causality**



## Complex Causes:

#### Synthetic Lethality





*Cell* 2011 144, 646-674DOI: (10.1016/j.cell.2011.02.013) Copyright © 2011 Elsevier Inc.

# Modeling Cancer

- *Model of Progression*: Based on a set of cross-sectional genetic alterations. Determine causal-structures.



**The ultimate goal** is to define progression-specific treatments using a derived causal model.

#### A Recent Article



#### Coming Full Circle—From Endless Complexity to Simplicity and Back Again

Robert A. Weinberg<sup>1,2,3,\*</sup> <sup>1</sup>Whitehead Institute for Biomedical Research <sup>2</sup>Ludwig/MIT Center for Molecular Oncology <sup>3</sup>MIT Department of Biology Cambridge, MA 02142, USA <sup>\*</sup>Correspondence: weinberg@wi.mit.edu http://dx.doi.org/10.1016/j.cell.2014.03.004

*Cell* has celebrated the powers of reductionist molecular biology and its major successes for four decades. Those who have participated in cancer research during this period have witnessed wild fluctuations from times where endless inexplicable phenomenology reigned supreme to periods of reductionist triumphalism and, in recent years, to a move back to confronting the endless complexity of this disease.

Cell

#### Cancer for Next Generation

**R** "How will all this play out?

"I wouldn't pretend to know. It's a job, as one says on these occasions, for the next generation. Passing the buck like this is an enormously liberating experience, and so I'll keep on doing it!"

--Bob Weinberg, Cell March 2014

### Big Data vs Big Mechanisms

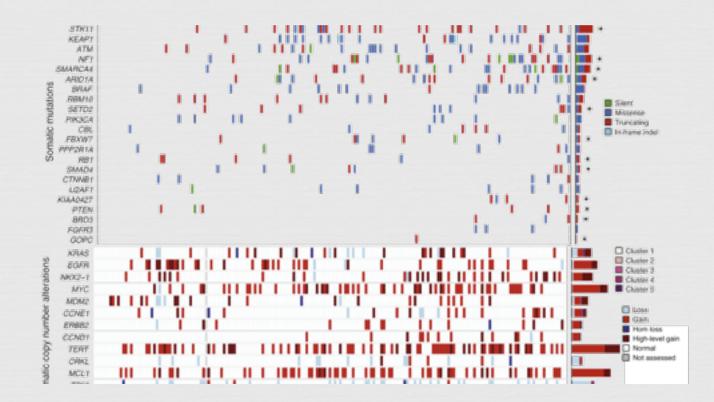
Can DARPA cure cancer?



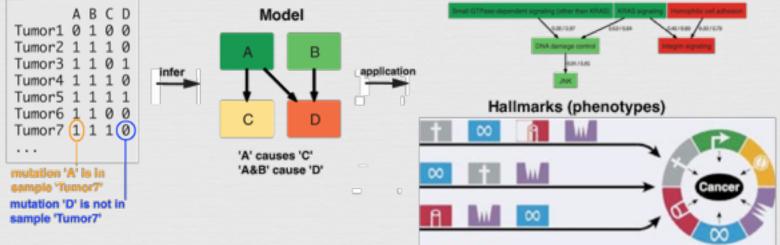
- Most cancer data currently available is **cross-sectional** (rather than "longitudinal")
  - It is collected from biopsies at time of diagnosis
  - Little follow up, time-stamped data (maybe collected, but not quite available)
- Inferring temporal information from cross-sectional data is challenging
- The problem has been studied in several fields, and in the context of cancer research since the late 90s

# Short & Fat Data

Lung cancer mutational profiles (cross-sectional) cfr., M. Imielinski et al., *Cell* 150, 2012



Input A B C D Input Model



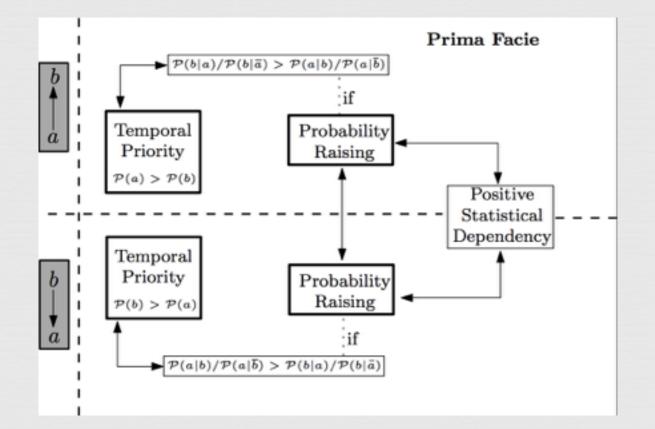
(adapted from) Gerstung et al., PLoS ONE, 6(11), 2011

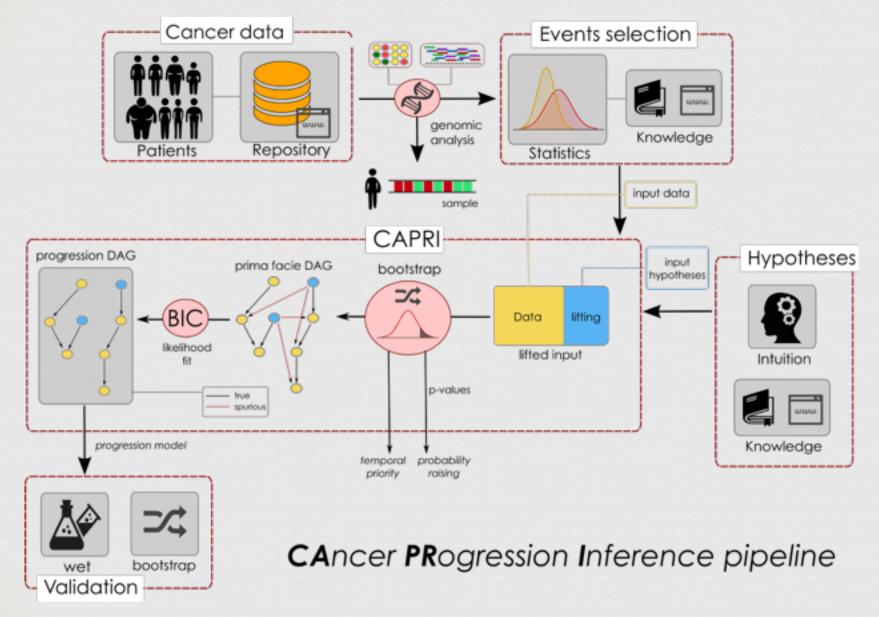


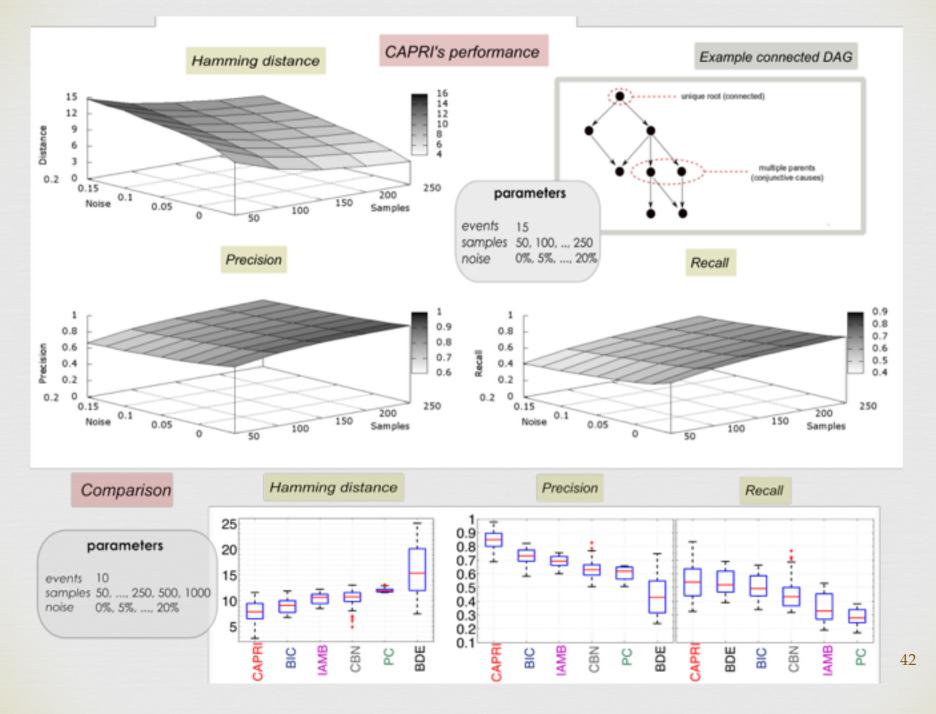
Models of Progression

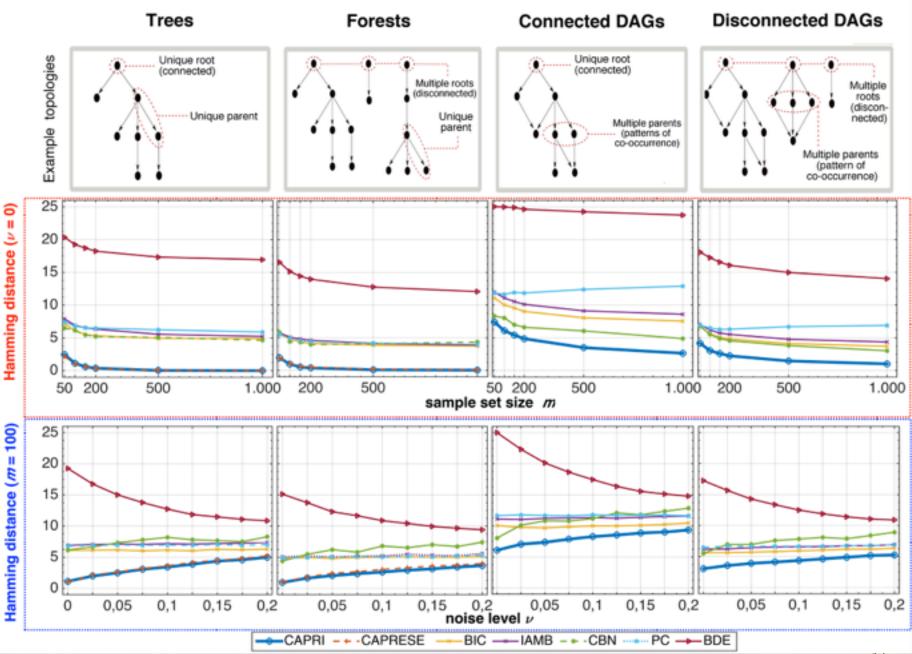
- Tree models
  - Desper, Papadimitriou Schäffer et al, 1999, 2000
- Conjunctive Models
  - Beerenwinkel, Sturmfelds et al, 2005, 2006, 2007
- Directed Acyclic Graph Models
- Correlation based models
  - Desper
- Bayesian models
  - Beerenwinkel

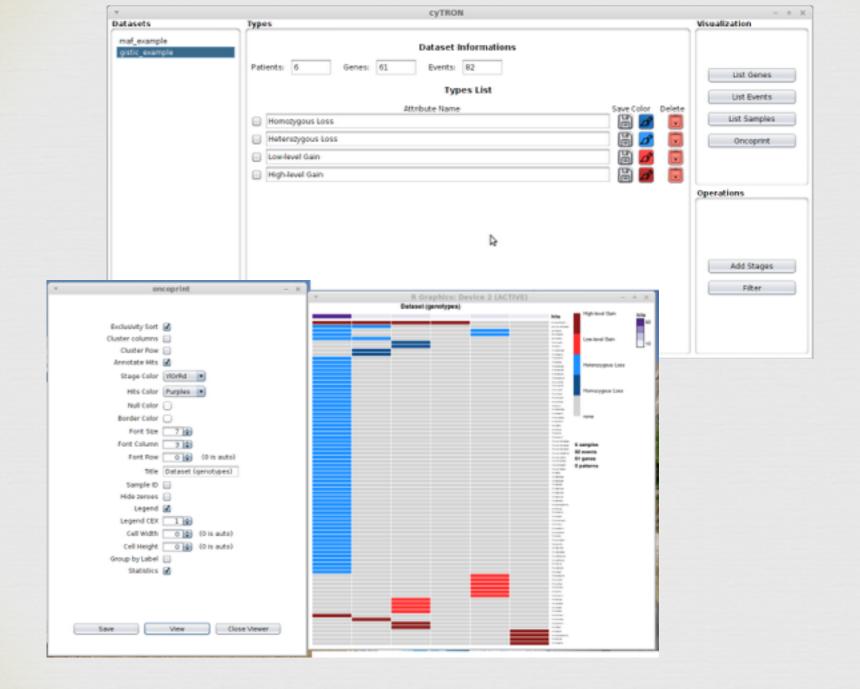
# The CAPRI Algorithm

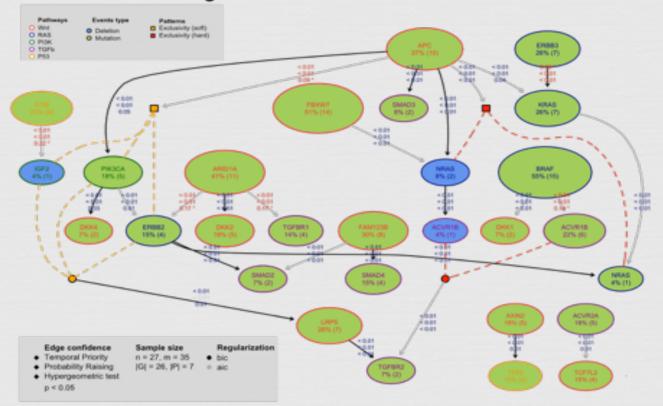




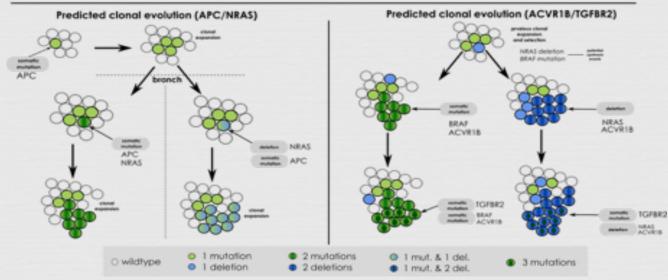


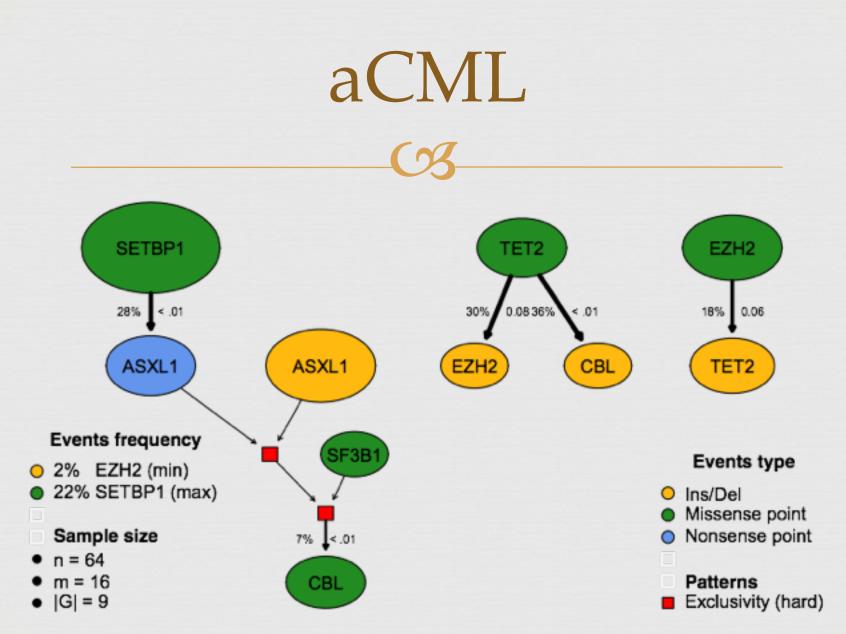






#### Selective advantage relations for TCGA MSI colorectal tumors





# Survival Analysis

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# Cox Regression

Hazard function for some feature vector X defined by baseline hazard and function of covariates.

 $h(X,t) = h_0(t) \cdot \exp\beta X$ 

Regression coefficients  $\beta$  can be learned by maximizing the log partial likelihood, ignoring the baseline hazard function.

$$pl(\beta) = \sum_{i} \delta(i) (X_{i}\beta^{T} - \log \sum_{j:t_{j} \ge t_{i}} \exp X_{j}\beta^{T})$$
  
$$\delta(i) = \begin{cases} 1 & observed \\ 0 & censored \end{cases}$$

# Fisher Kernel

The progression network defines a factorized form of the joint distribution in terms of conditional probabilities of features given their immediate parents in the graph.

$$Pr(X) = \prod_{i} Pr(X_i | Pa(X_i))$$

The practical Fisher kernel defines the similarity of two feature vectors with respect to a probability distribution.

$$K(X,Y) = (\nabla_{\theta} \log(Pr(X)))^T (\nabla_{\theta} \log(Pr(X)))$$

We use the progression network to define a practical Fisher kernel for the Kernel form of Cox's model.

$$K(X,Y) = (\nabla_{\theta} \log(\prod_{i} Pr(X_i | Pa(X_i))))^T (\nabla_{\theta} \log(\prod_{i} Pr(Y_i | Pa(Y_i))))$$

#### Fisher Kernel

#### L2 Cox

study ID	mean		standard error	study ID	mean		standard error
brca tcga	0.59	±	0.02	brca tcga	0.55	±	0.03
coadread tcga	0.56	$\pm$	$0.07^{**}$	coadread tcga	0.51	$\pm$	0.02
gbm tcga	0.55	$\pm$	0.02	gbm tcga	0.55	$\pm$	0.06
lgg tcga	0.67	$\pm$	0.05	lgg tcga	0.67	$\pm$	0.06
lihc tcga	0.58	$\pm$	0.02	lihc tcga	0.45	$\pm$	0.03
ov tcga	0.53	$\pm$	0.03	ov tcga	0.50	$\pm$	0.04
skcm tcga	0.48	$\pm$	$0.05^{*}$	skcm tcga	0.45	±	0.02

# Future: Progression & Therapy

### Challenges and Opportunities

- Single Molecule/Single Cell Technology:
  - Optical Mapping (OpGen, BioNano, etc.); Transcriptomics (MMC, Nanostrings, MRTech, etc.); Fluidics, ...

#### 

 Point-Mutations, Indels, Copy-Number, Rearrangements (Translocations, Inversions, etc.), Ploidy,...

#### Reterogeneity:

 Topological Data Analysis (Moduli-spaces & CAT(0), Persistent Homology, Modal Logic in Topological Spaces...)

#### 

 (Temporal Logic, Model Inference from CTCs & Cellfree DNA, Tissues of Origin,...)

#### **Rank** Therapy Design:

 Supervisory Control, Games against Nature, Epistemological models

#### Models of Cancer:

Signaling Games, Evolution Multi-cellularity,...

#### Technical Definition of Timed CHA

A timed state is a pair  $(v, val) \in V \times \mathbb{R}^{|X|}$ .

There are two types of transitions between timed states:

**1** Delay transitions, in symbols  $(v, val) \xrightarrow{\delta, C} (v, val')$ , where

- $\delta \in \mathbb{R}_{\geq 0}$  represents the (real) time delay,
- $C \in 2^D$  denotes the cocktail active during that time,
- $val'(x) = val(x) + \delta \rho(v, C, x)$  for all x, and
- $val'(x) \le l(v, x)$  for all x with l(v, x) defined.
- **2** State transitions, in symbols  $(v, val) \rightarrow (v', 0)$ , where
  - there is an edge  $(v, \phi, v') \in E$  with val  $\models \phi$

A therapy maps finite runs to cocktails:

 $\pi: \operatorname{Runs}_{\mathbf{f}}(H) \to 2^D$ 

Therapeutic regimens can be generated to ensure :

- avoidance of bad states (safety)
- general temporal goals (specified using variants of Computation Tree Logic - CTL)
- optimal cost

Therapies can be generated using algorithms from supervisory control.

Controller synthesis for untimed CHAs can be solved in (single) exponential time for CTL goals. For times CHAs, this problem is undecidable in the general case.

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# Thank you!

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# David Hume



Abstruse thought and profound researches I [*nature*] prohibit and will severely punish by the pensive melancholy which they introduce, by the endless uncertainty in which they involve you and by the cold reception which your pretended discoveries shall meet with, when communicated.

☆ "Be a philosopher, but, amid all your philosophy, be still a man."



