Causality Assessment with Multiple Time Series Data

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Intent

- DataSpeaks, Inc., an early stage growth company, offers a *uniquely digital measurement-by-computation tool* embodied in software
- It offers a disruptive measurement science solution
- Collaborate (research, grants, publications, etc.) to:
  - Help you – DCM&B, U-M, etc.
  - Advance DataSpeaks
  - Help solve the (i) bench to bedside and (ii) clinical science to clinical practice translation problems
  - Advance P4 Medicine

Causality Assessment

- Central to scientific understanding
- Focus on Complex Dynamic and Adaptive Systems (CDAS)
- Essential for basic and applied science (e.g., medicine)
- Two contexts for DataSpeaks' computational method
  1. Without randomized experimental control
     - HeLa cell cycle control – a human cancer cell line since 1951
     - Cancer – a failure of cell cycle control
  2. With randomized experimental control
     - Frequentist and Bayesian statistics not sufficient
     - Need Ultra RCTs (Randomized Controlled Trials) with DataSpeaks and statistics

Assessing causality with group average statistics on response variables is a failing paradigm. This makes it hard to translate from bench to bedside, protect patient safety, and achieve P4 Medicine. Together we can work toward a brighter future.

Time Series Data

- Here a shorthand for "periodic time-ordered data"
- Inclusive of:
  - Repeated measurements (< 20 repeats)
  - Time series (20 or more repeats)
  - Two or more repeats, hopefully many more
- Contrasts with cross-sectional data (including change scores)
- Time series can provide orders of magnitude more information to *understand individuals scientifically*
- Periodicity helpful for understanding temporal dynamics

➢ Please don't think that you must have time series as often defined to use DataSpeaks. It often applies when you can collect repeated measurements data.

➢ Do you think that it is possible to understand individuals scientifically?

➢ Science based largely on group averages is not designed to understand individuals scientifically.

➢ Personalized medicine calls for understanding individuals scientifically.

➢ Do we need time series to understand individuals scientifically?

The Great Bottleneck: We Need Better Computational Tools

Inputs:
- Omic sciences
- Data collection technologies
- IT infrastructure
- EHR

Outputs:
- P4 Medicine
- Safer medicine
- Better and more affordable health and healthcare
- Better drugs to market faster
- New drug indications

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DCM&B can help overcome this bottleneck. My impressions are that tranSMART (http://www.transmartproject.org/) has related objectives and that DataSpeaks should be part of tranSMART.

What problem could not be done better with multiple time series?

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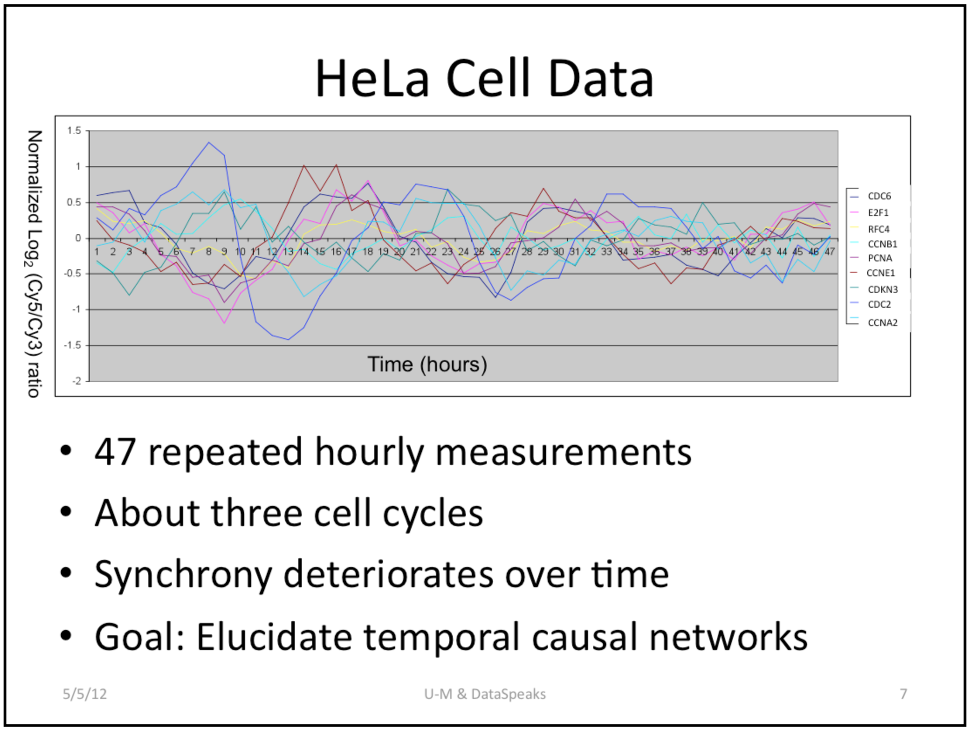
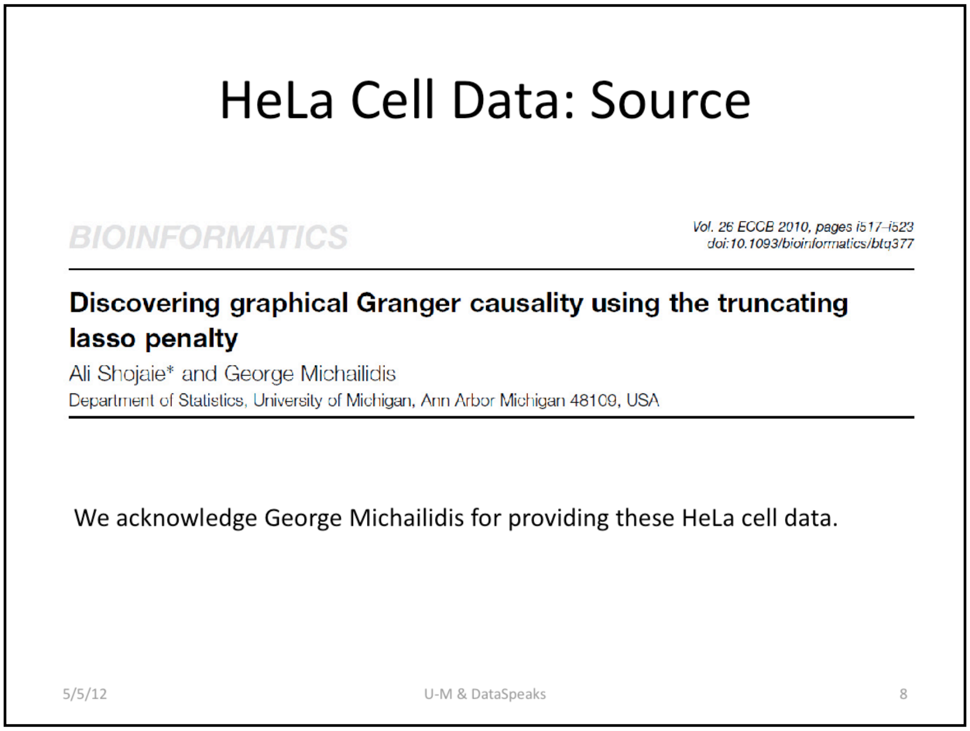
Please consider how you might be able to use this tool. When might it be helpful? When is it not? We will return to this question.



Extract scientific information about causality from such spaghetti piles of time series data – what causes what?



Walter, Alex, and I meet with George for almost two hours before this presentation. We are planning to meet again during the first week in June after he returns from lecturing in Paris.

Granger Causality

- If “a signal X_1 "Granger-causes" (or "G-causes") a signal X_2, then past values of X_1 should contain information that helps predict X_2 above and beyond the information contained in past values of X_2 alone.”
- “Its mathematical formulation is based on linear regression modeling of stochastic processes.”
- This won Clive Granger the 2003 Nobel Prize in Economics
- One application of DataSpeaks is a *measurement* alternative to Granger causality, not a variation

➢ A second time series can help predict a first above and beyond past values of the first alone.

➢ Granger causality is a linear method.

HeLa Cell Data: History

Molecular Biology of the Cell
Vol. 13, 1977–2000, June 2002

Identification of Genes Periodically Expressed in the Human Cell Cycle and Their Expression in Tumors

Michael L. Whitfield,[*] Gavin Sherlock,[*] Alok J. Saldanha,[*] John I. Murray,[*]
Catherine A. Ball,[*] Karen E. Alexander,[†] John C. Matese,[*]
Charles M. Perou,[‡] Myra M. Hurt,[†] Patrick O. Brown,[§||¶] and
David Botstein[*¶]

- Whitfield, M. *et al* uses clustering methods
- Same HeLa cell data subject of other publications with various methods in addition to Shojaie/Michailidis
  - Lozano *et al* - 2009 (Grouped Graphical Granger Modeling)
  - Sambo *et al* – 2008 (CNET)
  - Sacchi *et al* – 2007 (Precedence Temporal Networks)

DataSpeaks

- Offers uniquely digital measurement-by-computation algorithm embodied in software
- MQALA (Method for the Quantitative Analysis of Longitudinal Associations)
- Applies to multiple time series data
- Measures the (i) amount, (ii) positive or negative direction and (iii) strength of evidence for coordination of action

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Alternate terminology for “coordination of action” includes “interaction-over-time” and “longitudinal association.” Benefit and harm scores are a variation of these scores for evaluative investigations such as RCTs.

DataSpeaks, continued

- Coordination scores (CS) describe and help predict how *individual* CDAS *work* over time
  - Function internally (e.g., HeLa cell cycle control)
  - Respond to environments including treatments (e.g., Ultra RCTs)
  - Act as agents on their environments (neglected stepchild of science)
- Bagne holds two issued U.S. software patents
  - 6,317,700 – Method and System to Perform Empirical Induction
  - 6,516,288 – Method and System to Construct Action Coordination Profiles
- Software available as a functional prototype, open to additional collaboration and project discussions
- Dennis Nash heads business development dnash@dataspeaks.com
- Collaborating with U-M through Brian Athey

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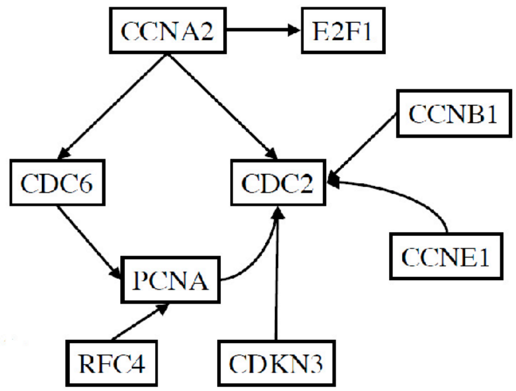
➢ Statistics is a well known method of "empirical induction." DataSpeaks is another.
➢ "Action coordination profiles" measure coordinated action as an emergent system property. Empirical scientific understanding is based on measurement.

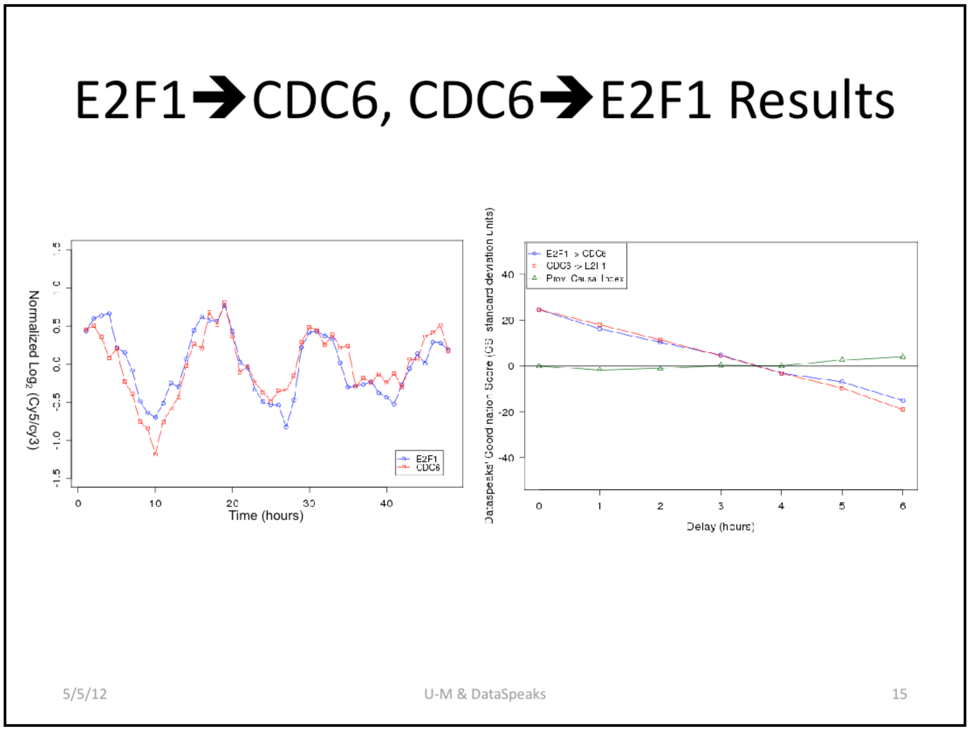
DataSpeaks' Approach: Causality Assessment with HeLa Cell Cycle Control Data

- Nine genes, cancer activators
- 72 pair-wise directional interactions over time
  (e.g., CDC6➔CDC2, PCNA➔E2F1) [➔ operates on]
  [independent variable (IV) ➔ dependent variable (DV)]
- 36 pairs (e.g., PCNA➔CDC2, CDC2➔PCNA; CDKN3➔CDC2, CDC2➔CDKN3)
- *Measure temporal asymmetries* within each pair using DataSpeaks' Coordination Scores (CS)
- Causes must come before effects – the temporal criterion of causal relationships

“Known” Network



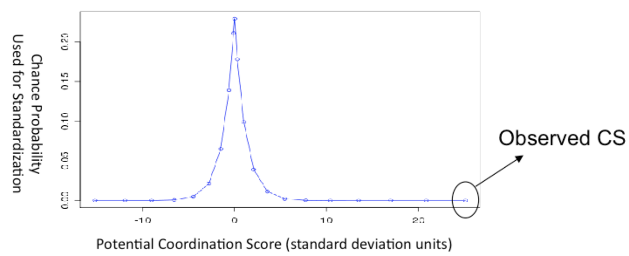
- “Known” network from Sambo, et al 2008
- Extracted from www.thebiogrid.org
- Cited by Shojaie/Michailidis as “Known Regulatory Network”



- ➢ The left-hand figure shows expression levels for two genes.
- ➢ The right-hand figure shows three lines. The blue line shows Coordination Scores (CS) when E2F1 is selected to function as the IV. The red line shows CS when CDC6 is selected to function as the IV. The green line shows differences between these two lines. These differences are taken to provide evidence for temporal asymmetry that can provide some evidence for causality when IV are not under randomized experimental control. This green line shows values for the "Provisional Causal Index." [Two differences are possible depending on the order of subtraction. By convention for these slides, green lines show the set of differences for which the most extreme value is positive.]
- ➢ This slide shows strong evidence for a positive association that is not causal as indicated by a green line that hovers near y = 0. This green line quantifies temporal asymmetries. DataSpeaks welcomes collaborators to further develop, refine, and advance this index. One opportunity for further development is to use signs to distinguish genes functioning as activators from genes functioning as suppressors.

Meaning of Coordination Scores

- Coordination - “harmonious functioning of parts for effective results”
- The CS at Delay = 0 in the previous slide is 25.123
- CSs are in standard deviation units
- 25.123 is one score in the following distribution of potential scores



- We will introduce you to computing these scores after several more results

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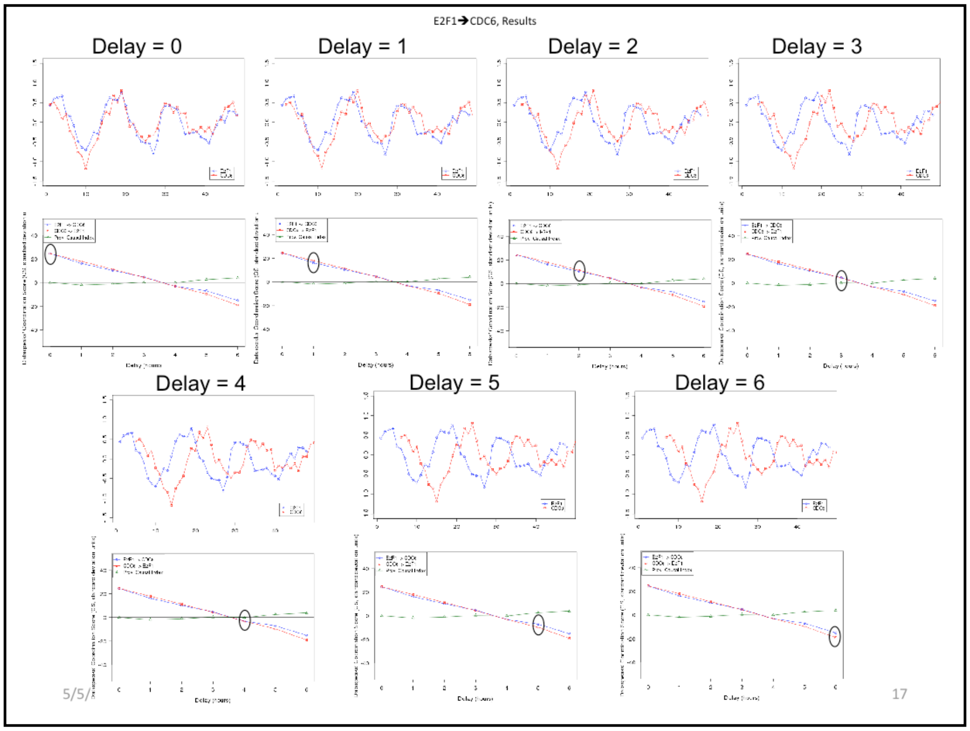
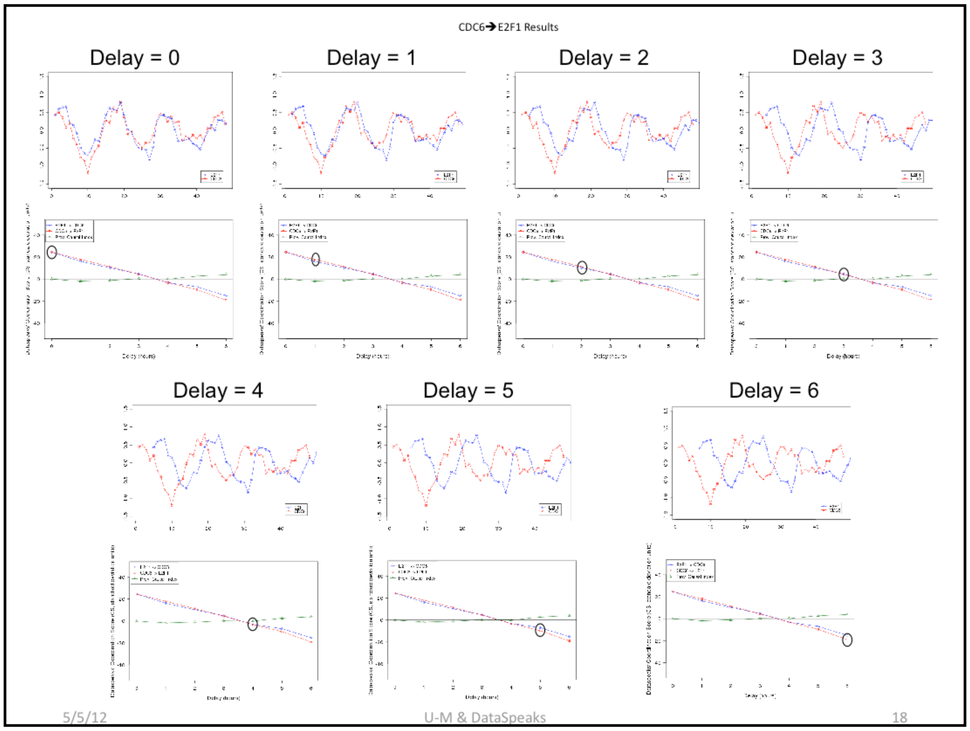
➢ Distributions of potential scores are defined by the data in combination with an operationally defined DataSpeaks’ scoring protocol. Protocols are defined by selecting menu options in DataSpeaks’ software.
➢ The probability of the observed score is 1.25×10^{-12}. These hypergeometric probabilities are used to help compute standardized scores. These probabilities must **not** be interpreted as levels of statistical significance.

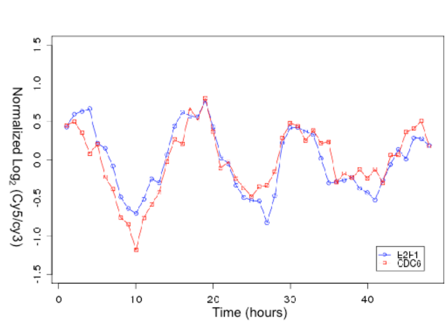


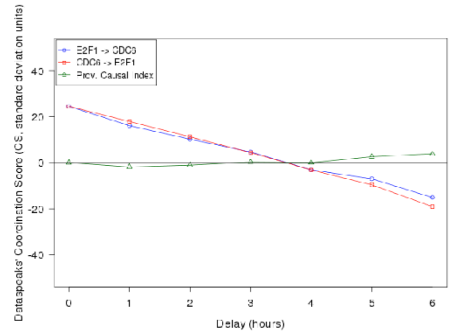
These graphs are intended to help viewers understand what DataSpeaks measures and how these measures are affected by Delay. Delay is one of 8 analysis parameters built into the current version of DataSpeaks' software. This set of 7 graph pairs shifts the red line in the corresponding data slide hour by hour to the right to illustrate Delay. At Delay = 0, peaks line up with peaks and troughs line up with troughs. This is quantified with a large positive CS. At Delay = 6, peaks and troughs are almost entirely offset. This yields a substantial negative CS. Values in between yield intermediate coordination scores.



This set shifts the blue line hour by hour to the right to illustrate Delay.

E2F1➔CDC6, CDC6➔E2F1 Results





- Not a “known” interaction
- Apt to be clustered together but not causal
- DataSpeaks - almost no evidence of causality (green line)
- Not identified by Shojaie/Michailidis

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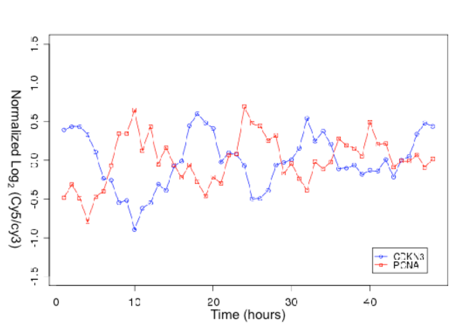
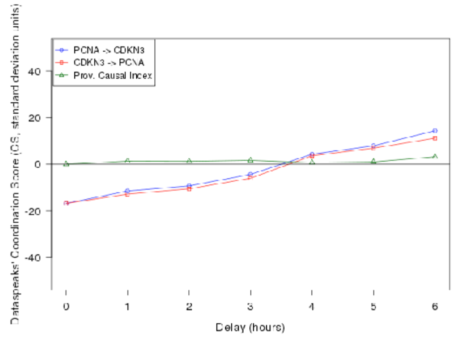
This shows strong evidence for a **positive** association that is not causal. With DataSpeaks, associations are labeled positive or negative by signs of the most extreme standardized scores from DataSpeaks.

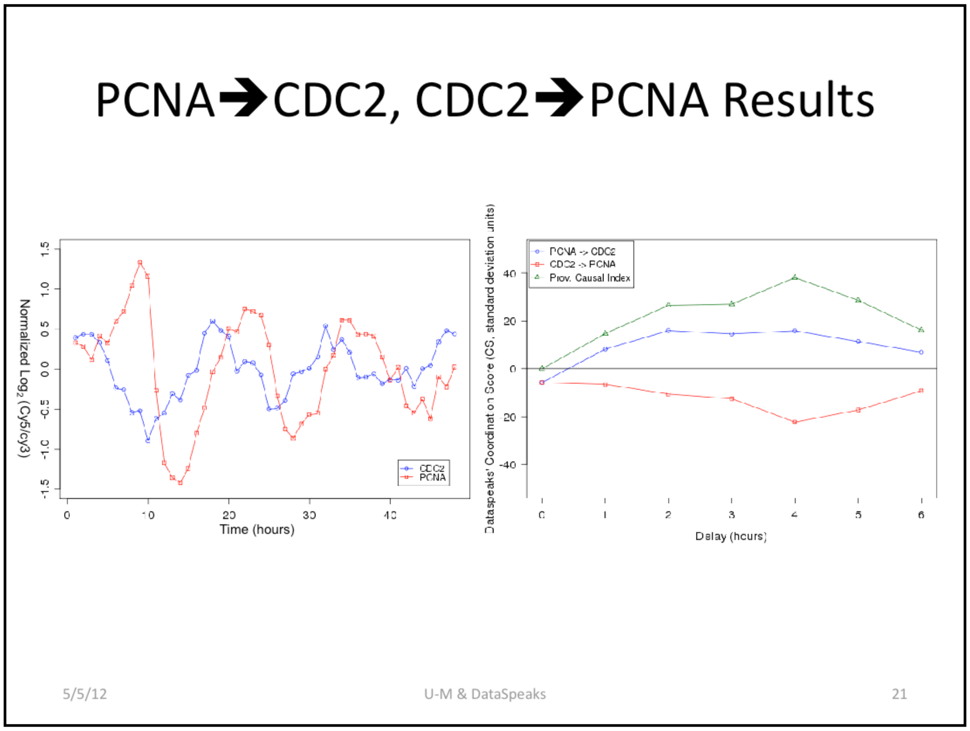
PCNA➔CDKN3, CDKN3➔PCNA Results



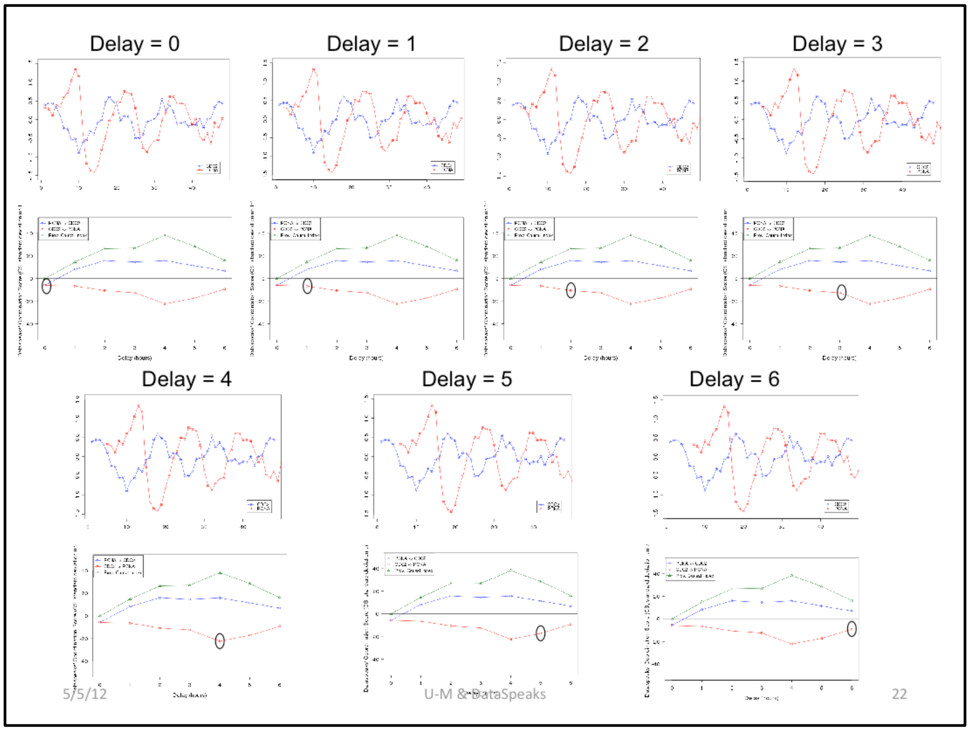


- Not a “known” interaction
- DataSpeaks - almost no evidence of causality (green line)
- Not identified by Shojaie/Michailidis

This second example provides strong evidence for a **negative** association that is not causal.



Unlike the previous two examples, this example provides strong evidence for causality as indicated by the green line deviating widely from y = 0, especially at Delay = 4.


Delay = 0
Delay = 1
Delay = 2
Delay = 3
Delay = 4
Delay = 5
Delay = 6
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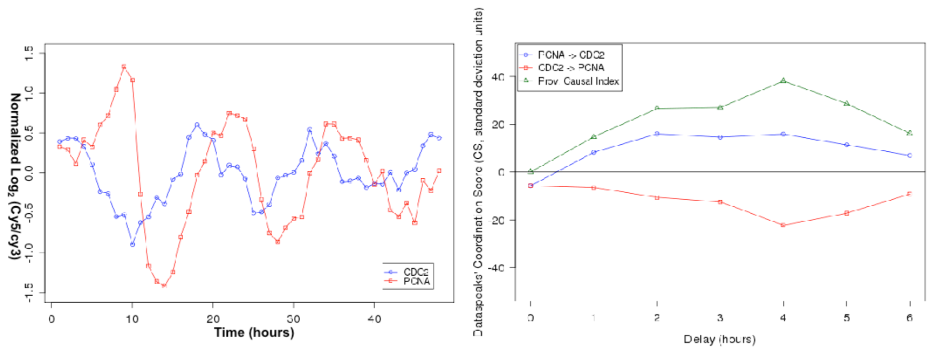
PCNA➔CDC2, CDC2➔PCNA Results



- This is a “known” interaction
- DataSpeaks identifies strong evidence for causality
- Not detected by Granger causality as reported by Shojaie/Michailidis

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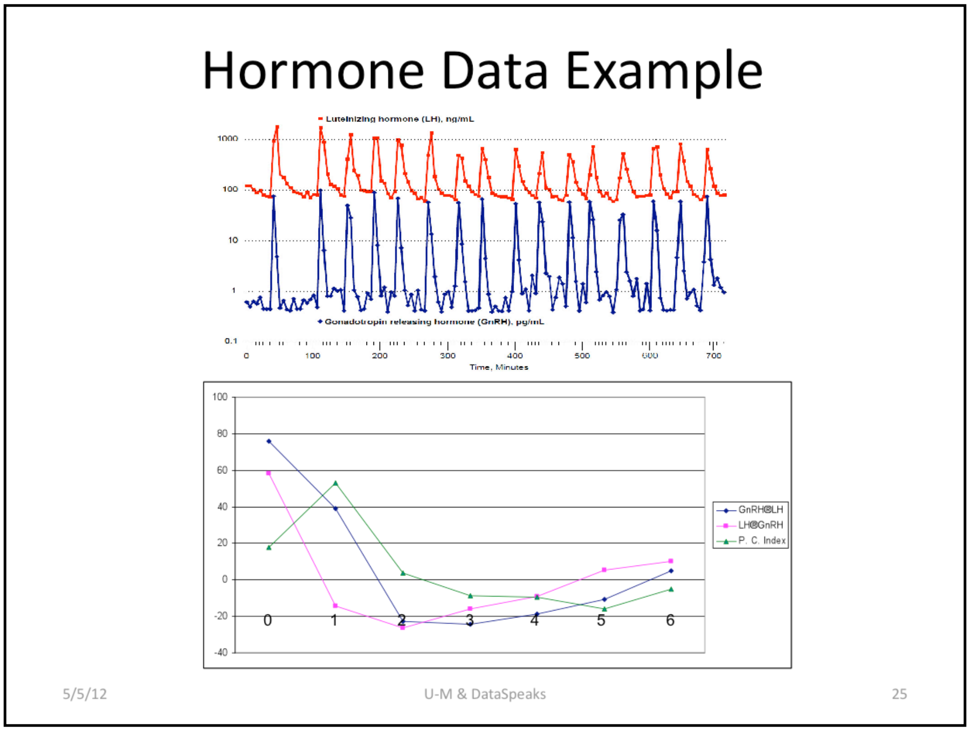
Unlike the previous two examples, this example provides strong evidence for causality.

Results Summary: Comparison by Method

- This is summarized in a handout



➢ Both hormones were measured from portal blood (where the hypothalamus interacts with the pituitary gland) every 5 minutes for about 12 hours in a ewe (female sheep) at U-M.

➢ It is well known that GnRH controls LH. These results help to validate DataSpeaks. DataSpeaks provides strong evidence (green line in bottom graph) for a causal relationship. Furthermore, the fact that the CSs are larger for GnRH to LH at short delays (0 and 1) than for the LH to GnRH suggests that the direction of causality is from GnRH to LH, not vice versa. This appears to further validate DataSpeaks. DataSpeaks appears to provide evidence for causality where this is difficult to perceive visually.

Major Steps to Compute and Use DataSpeaks' CS Scores

1. Optional data pre-processing
2. Convert each dimensional series into a set of digital series
3. Form additional digital series to account for delay, persistence, episodes, Boolean events
4. Cross-classify each digital series for an IV or predictor variable with each digital series for for an DV or predicted variable to form arrays of 2x2 tables
5. Compute a raw CS for each 2x2 table
6. Compute a standardized CS for each 2x2 table
7. Summarize standardized CS scores
8. Analyze results statistically when there are groups of two or more individuals

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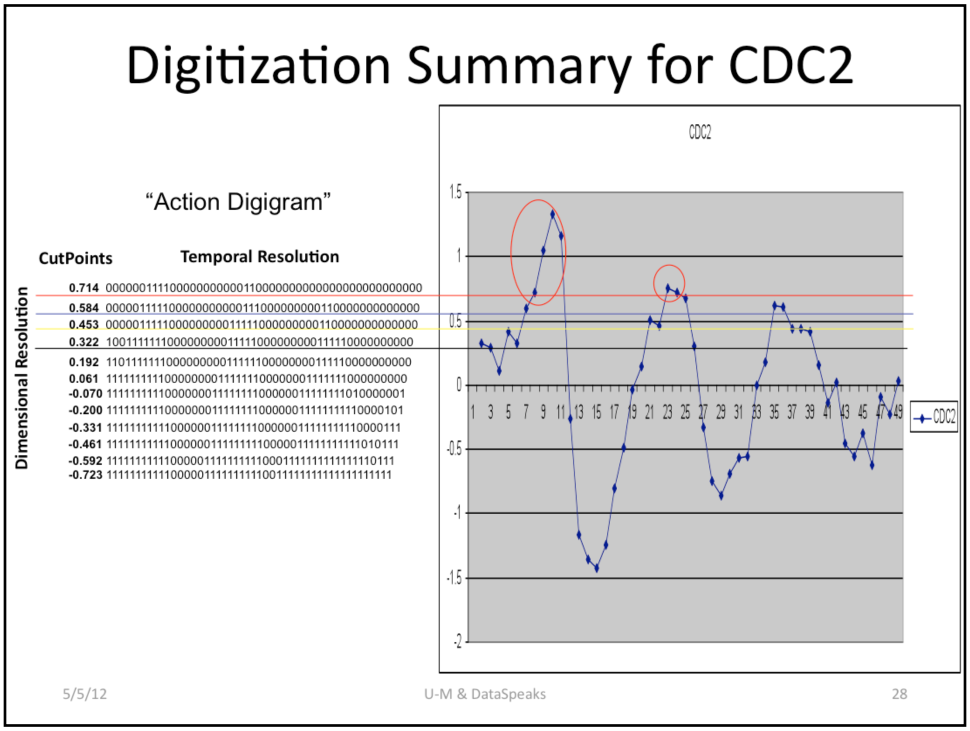
➢This is published and included in my patents.

➢ Step 1 allows software users to select from among a variety of data pre-processing options. One option is to process data as residuals from linear trend. The value of this has been demonstrated by applying DataSpeaks to economic time series when the task to to predict periods of relative recession or prosperity in a generally growing economy. The current version of DataSpeaks also can process data as residuals from polynomial regression up to the sixth order. Overfitting time series drives down the resulting CSs. Another option is to process the data using successive differences in repeated measurements. This has proven useful processing time series for ACTH and cortisol. Here successive differences were far more predictive than hormone levels.

➢ Please do not confuse DataSpeaks' measurement technology with statistics.

Step 2: Digitization

- One key to DataSpeaks' capabilities
- Required when a time series has more than two levels
- *Digitization has potential to be as valuable for understanding individuals scientifically with time series as digitization has been for photography and communications.*
- Individuals can be cells, brains, people, whole populations, economies, Earth's biosphere, etc.

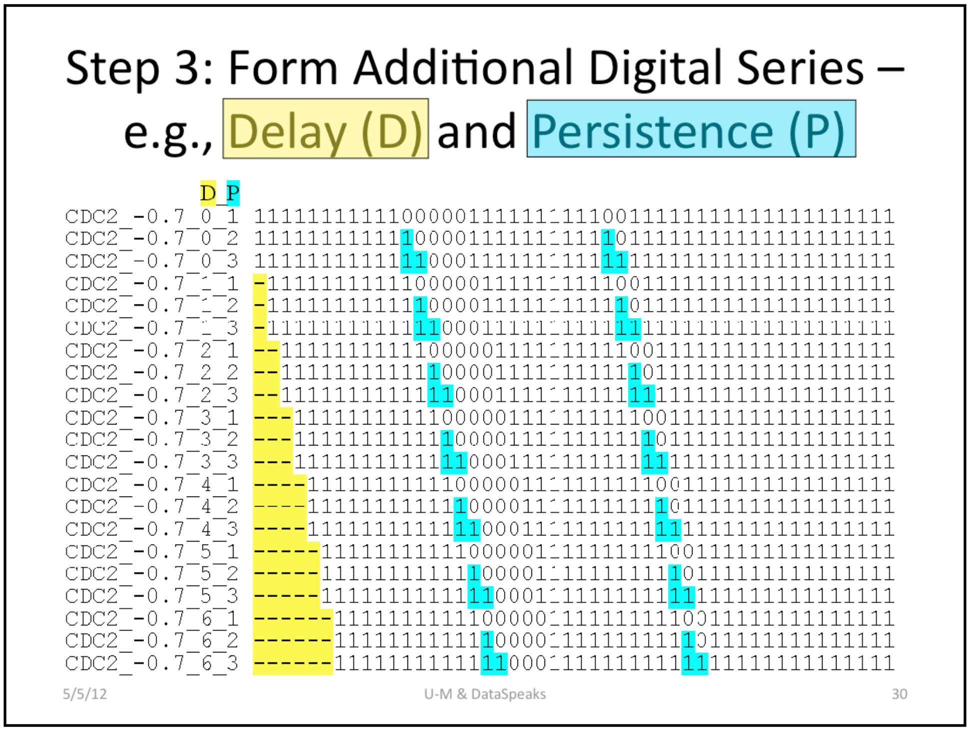


- ➢ See the pattern in the action digigram.
- ➢ Has anyone seen this done before?

Value of High Resolution – Temporal and Dimensional

- Better resolution of DataSpeaks for understanding *dynamic temporal phenomena* is related to better resolution in digital photography.
- An aspect of *DataSpeaks' data microscope* – see patterns that have never been seen before
- Biggest gains apt to come from improving temporal resolution.
- *Statistics gains power with more subjects.*
- *DataSpeaks gains power with more repeated measurements.*
- **Big Data** – Really gain power with more subjects AND more repeated measurements AND higher resolution.

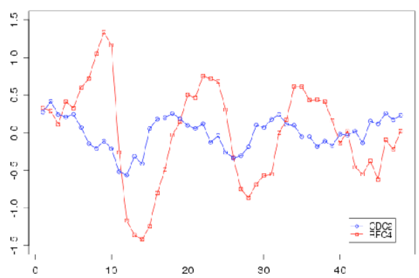
Many RCTs use a temporal resolution of two – baseline and endpoint.

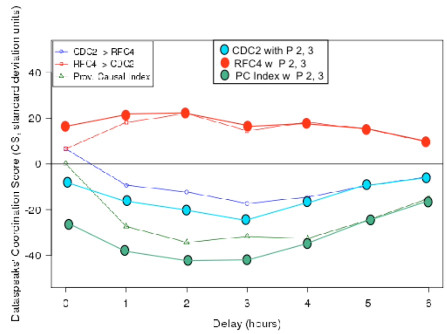


Various methods use time-lagged cross-correlations to assess what I call delay. However, there is much more to understanding effects of time than just delay. This illustrates how we can define additional digital series to investigate both delay and persistence.

Illustrate with drug doses. Absorption and other processes can affect build up of drug in blood and target tissues. Additional processes such as metabolism and excretion can affect persistence. To some extent, delay and persistence might be independent. DataSpeaks can investigate both delay and persistence.

RFC4→CDC2, CDC2→RFC4
Delay and Persistence





➢ The default value for persistence is 1. This shows DataSpeaks' results using two additional optional values for persistence, 2 and 3. Adding additional analysis parameters and levels of analysis generally increases the magnitudes of CSs.

➢ Note that values of the Provisional Causal Index at Delay = 0 are always 0 when no other temporal analysis parameters are selected for use in the scoring algorithm. Here this index can be substantially different from 0 because of the use of an additional analysis parameter, persistence. [Unlike other slides in this set, this slide shows large negative values of the Provisional Causal Index in a situation where absolute values count.]

➢ According to the known network, RFC4 acts on CDC2 through PCNA. This result seems to make sense.

Capabilities to Define Digital Events: DataSpeaks' Software Currently

- Independent events
  - 12 levels of dimensional resolution
  - 7 levels of Delay, 0 – 6
  - 5 levels of Persistence, 1 – 5
  - 36 combinations of Episode Length and Episode Criterion
  - 15,120 (12x7x5x36) total combinations
- Dependent events
  - 12 levels of dimensional resolution
  - 36 combinations of Episode Length and Episode Criterion
  - 432 (12x36) total combinations
- Superb for pattern finding

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15,120x432=6,531,840. This is the number of scores in 8-dimensional arrays can can be computed when the current version of DataSpeaks' software is used with computers that have adequate virtual memory.

Boolean Independent Events for Complexity

- Assess *multiple causes*, e.g. multiple levels of:
  - Gene activity, proteins, lipids, carbohydrates, metabolites
  - Electrophysiological variables, brain activity
  - Drugs – an alternative to usual way of investigating drug/drug interactions
- Also can do Boolean dependent events for syndromes
  - Multiple signs and symptoms of disease and disorder
- An antidote for reductionism?

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Drug/drug interactions become Boolean independent events that can be assessed within individuals with DataSpeaks.

Example: Boolean Independent Events

- PCNA_0.2_1_1_0_1
  111110000000000011110000000000011100000000000111
- CCNA2_0.1_1_1_0_1
  000001111111000000110111110000000111111101000001
- PCNA_0.2_1_1_0_1 AND CCNA2_0.1_1_1_0_1
  000000000000000000110000000000000100000000000001
- PCNA_0.2_1_1_0_1 OR CCNA2_0.1_1_1_0_1
  111111111111000011110111110000011111111101000111

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➢ Can be extended to more Boolean operations and more time series to investigate substantial complexity.

➢ This example largely is copied from DataSpeaks' software.

Step 4: Cross-Classify Digital Series to Form an Array of 2x2 Tables

- Cross-classify each digital series for an IV with each digital series for a DV

		IV Present	IV Absent	
		1	0	
DV	Present, 1	1, 1 *a* 23	0, 1 *b* 4	27
	Absent, 0	1, 0 *c* − 17	0, 0 *d* − 4	21
		40	8	

- Example:
- PCNA_-0.4_1_1_0_1 111111100000111111111111000111111111111111111111
- CDC2_0.1_1_1 110111111100000000111111100000011111111010000101
- *aacaaaabbbddccccccaaaaaabddccccaaaaaaaacaccccaca*
- Yields 3-D array of 12x12x7=1008 2x2 tables for each gene pair for these examples

Step 5: Compute Raw Coordination Scores

- Start with observed 2x2 table
- Compute chi square
- Set sign
  - Compute expected value of *a*, E(*a*)
  - If observed value of *a*, O(*a*), is < E(*a*), then raw CS is negative chi square to indicate negative CS
  - If O(*a*) is > E(*a*), then raw CS is positive chi square to indicate positive CS

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DataSpeaks would welcome help to define a more mathematically elegant and perhaps more computationally efficient version of this algorithm that yields scores with the same values.

Step 6: Compute Standardized Coordination Scores

- CSs must be standardized
- DataSpeaks standardizes these scores to have an expected value of 0 and a standard deviation of 1.
- How? What is the trick?

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Standardization is imperative for DataSpeaks. Standardization facilitates comparisons. DataSpeaks is not a rubber ruler!

Standardization Example

		Raw Score	P(Raw) Score	Standardized Score
19	8	-7.466667	0.00588335	-4.363133
21	0			
20	7	-3.809524	0.0494201	-2.231321
20	1			
21	6	-1.371429	0.164734	-0.810112
19	2			
22	5	-0.152381	0.284540	-0.099508
18	3			
23	4	0.152381	0.278354	0.078143
17	4			
24	3	1.371429	0.157734	0.788747
16	5			
25	2	3.809524	0.0504749	2.209955
15	6			
26	1	7.466667	0.00832004	4.341767
14	7			
27	0	12.342857	0.000539262	7.184184
13	8			

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The marginal frequencies of the observed 2x2 table can be used to identify a mutually exclusive and exhaustive set of all possible 2x2 tables that are possible given these marginal frequencies. These are hypergeometric probabilities that also are used in the Fisher exact test. Compute the mean and standard deviation of the raw scores and use these to compute the standardized scores. Here E(a) = 22.5.

If any marginal frequency is 0, the only possible CS is 0 and the standard deviation of the potential scores is 0.

Step 7: Summarize Standardized Coordination Scores

- Select CS score with the highest absolute value to summarize
  - Each whole array
  - Any array dimension (e.g., IV level, DV level, delay, persistence, episode length, episode criterion)
  - Any combination of dimensions
- Locations of summary scores identify conditions that yield most evidence for coordination

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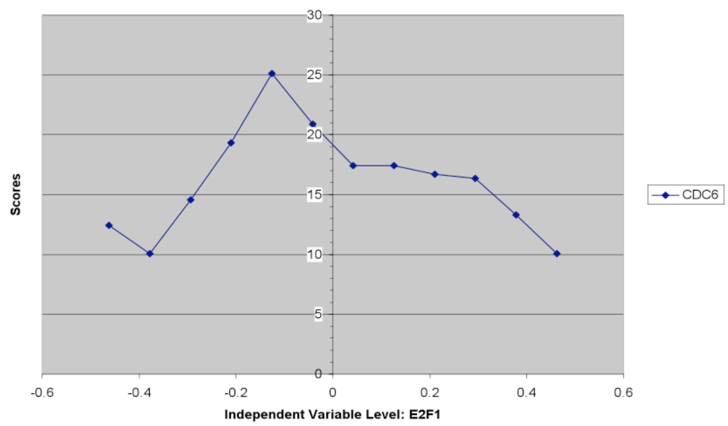
The examples that I showed you summarized CSs as a function of Delay. These are what we used to evaluate the temporal criterion of causal relationships.

CSs Summarized as Function of IV Level at Delay = 0

- Does DataSpeaks address non-linearity?



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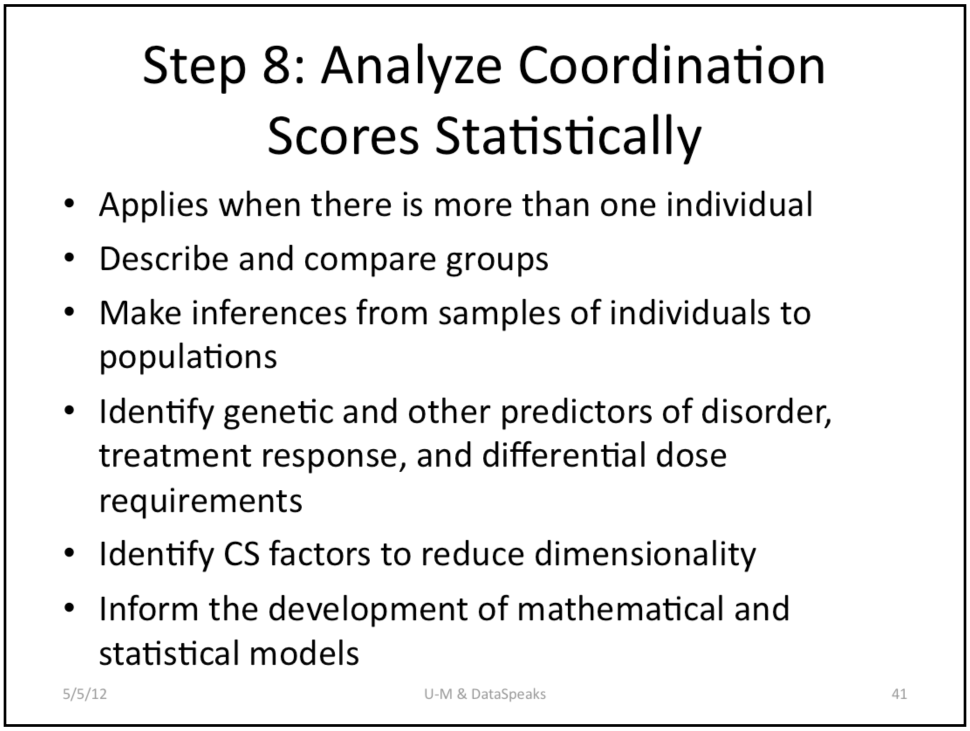
➢ DataSpeaks makes it possible to investigate CSs as functions of level of each of the time series. This appears to be a unique capability. Can you do anything like this with statistical measures of correlation?

➢ It appears as if DataSpeaks has great potential to investigate non-linear relationships. Again, DataSpeaks welcomes collaborators to help investigate this further.



- DataSpeaks measures individuals. Statistics describes groups and makes inferences from samples of individuals to groups. It is important to keep these two distinct.
- Measurement of CSs has been the missing step.

DataSpeaks Elucidates Mechanisms

- For example, grow any of over 100 cell lines under different environmental conditions
  - Temperatures
  - Different cell culture media reagents and supplements
  - Actual or potential anti-cancer drugs in media
- Visualize detailed information about how coordination might be affected

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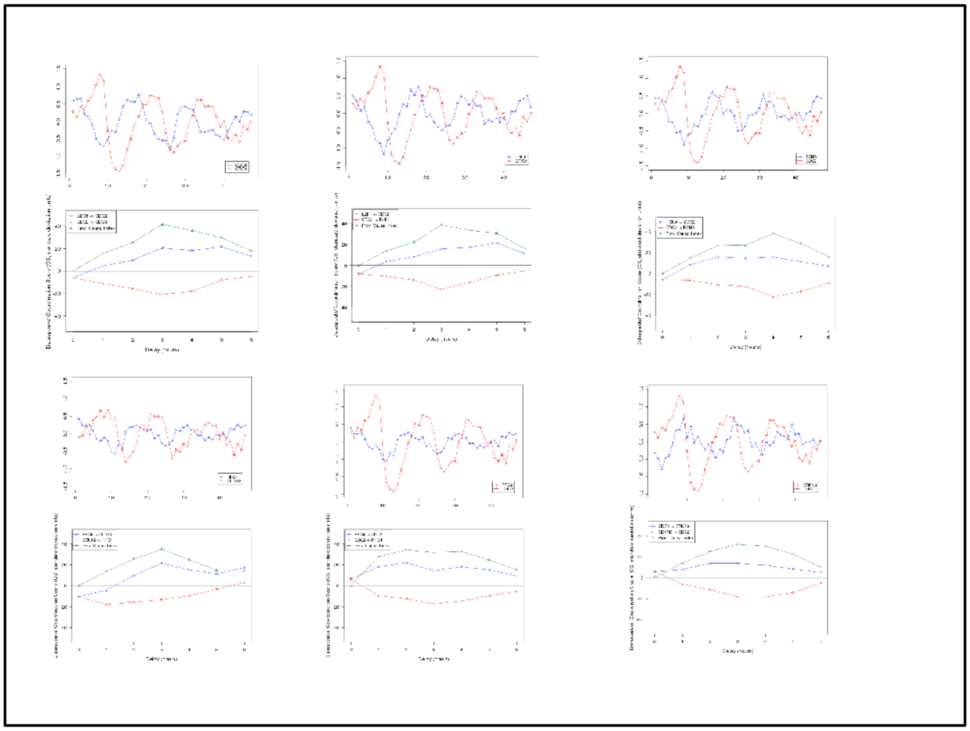
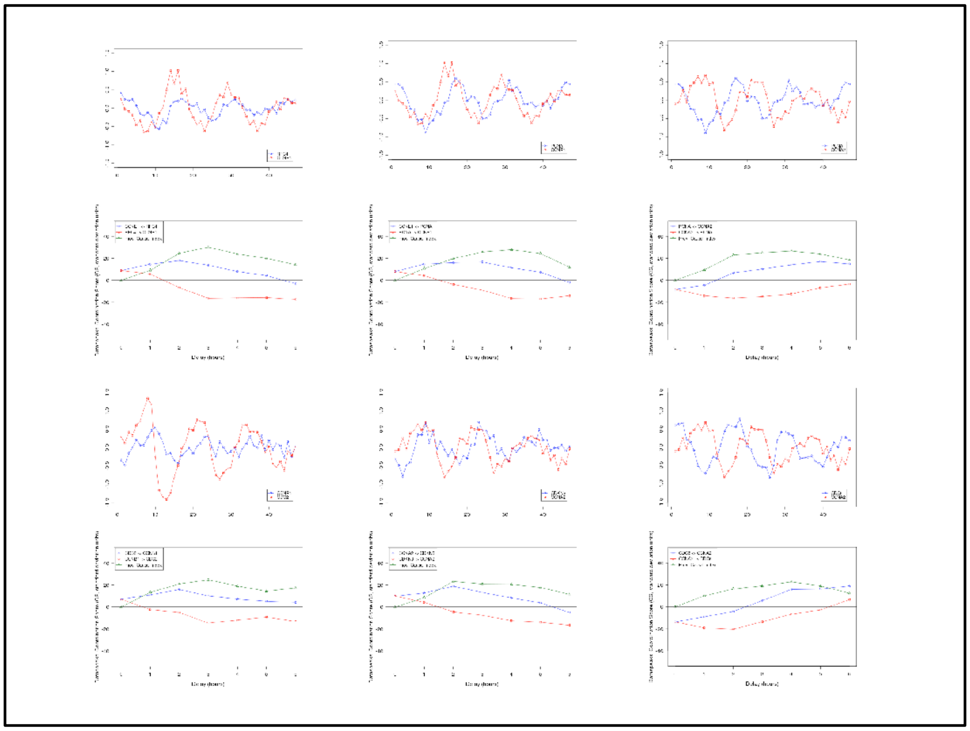
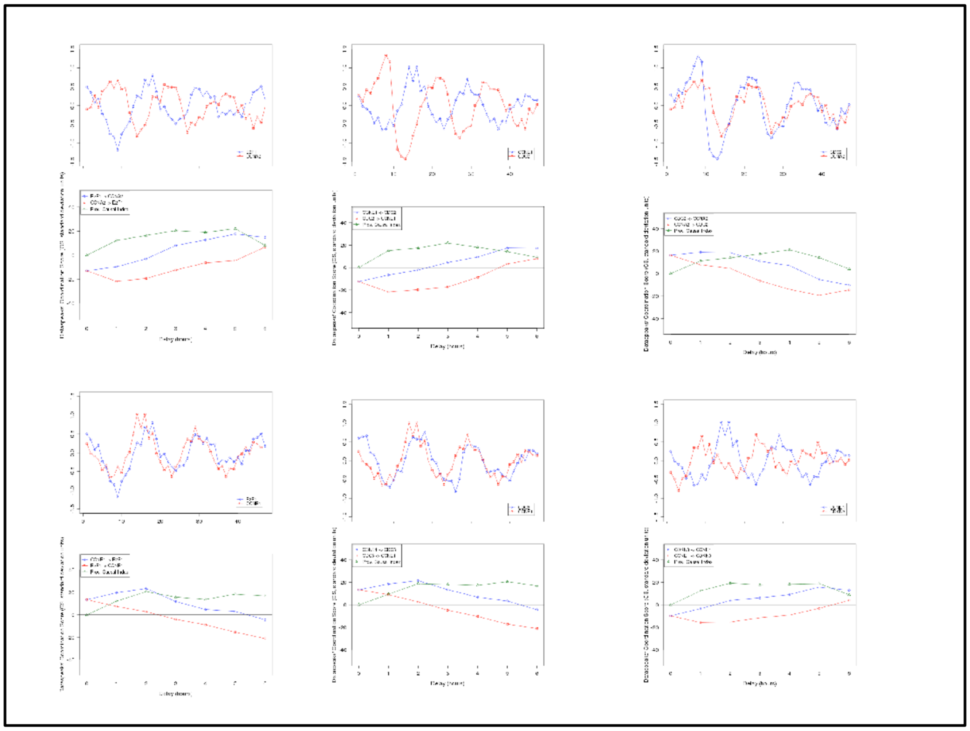
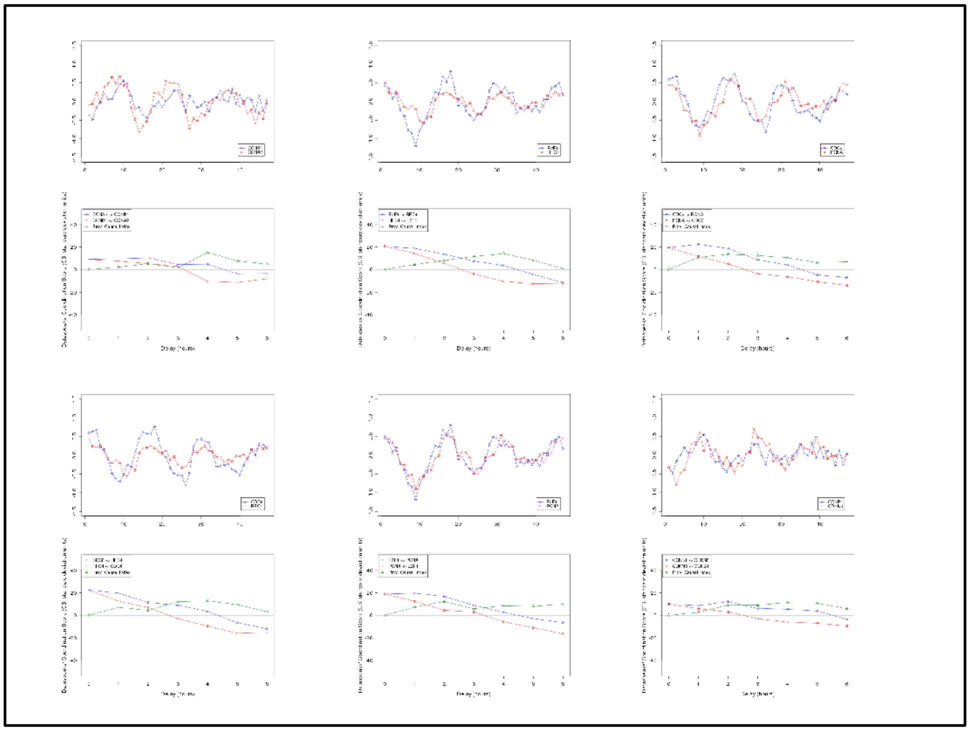
This might help to cure some cancers.

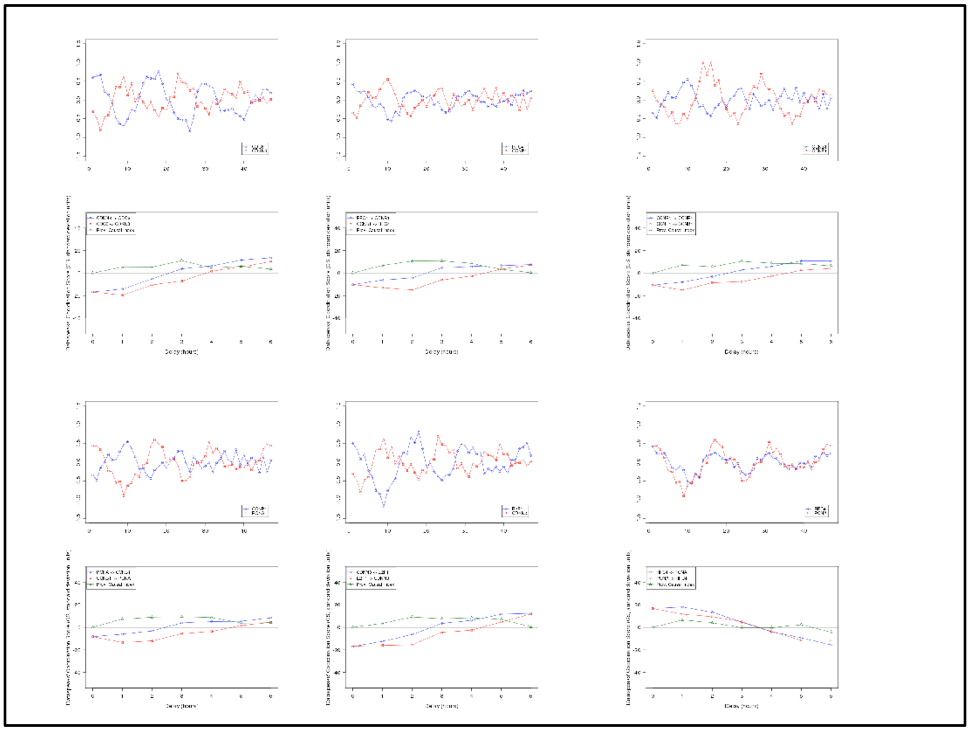


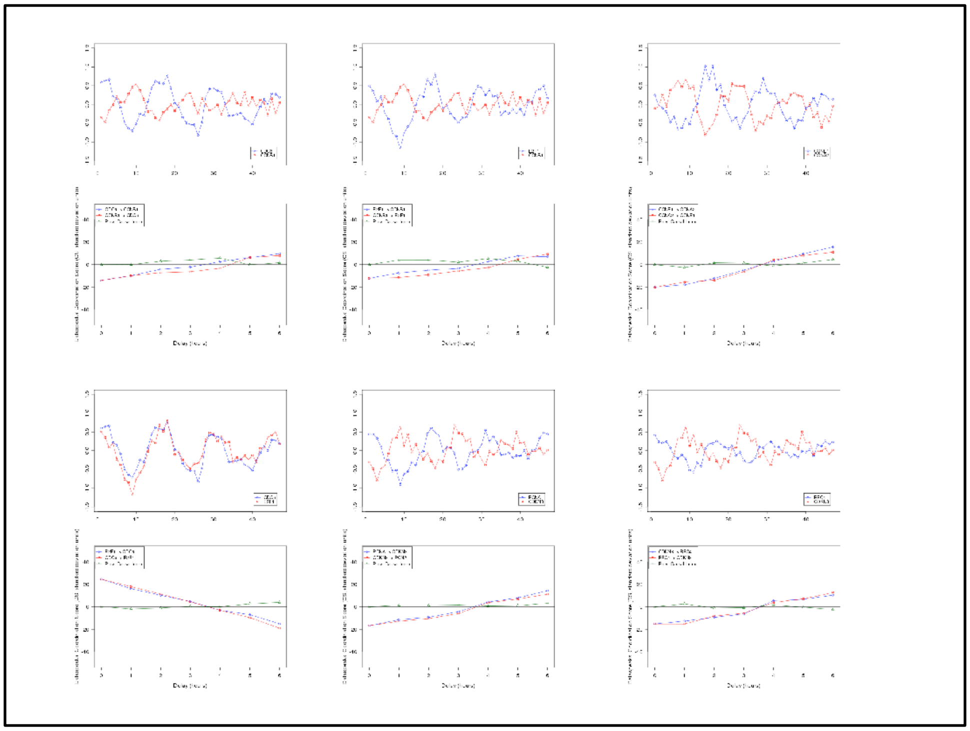
This and the following set of 5 slides show results for all 36 pairs as identified in Slide 13. Suppose we add a potential cancer drug to the growth media for these cells and rerun the study. Then it would be possible to difference any of these results to observe how the drug might affect any or all of these results. It appears that this could help elucidate mechanisms of drug effect on cell cycle control.











DataSpeaks Will Advance Medical Diagnosis

- Many chronic health problems appear to be *disorders of coordinated action* at various levels
  - Biological (proteins, lipids, carbohydrates, metabolites, electrophysiological, etc.)
  - Psychological (mental and physical behavior)
  - Social (e.g., family and work role performance)
- Coordinated action is an emergent system property
- Dream project: Apply DataSpeaks to BOLD fMRI data to visualize disorders of functional connectivity between and among brain regions

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BOLD fMRI data are readily and publically available. 15 minutes of scanning would yield about 450 repeated measurements. Voxels are spatially localized. This facilitates visualization of results. We have potential to essentially create a new imaging modality by adding a module of DataSpeaks' software to existing machines. The value proposition is to improve people's lives with more specific and actionable diagnoses of many chronic neuropsychiatric disorders.

Let’s Rock the RCT Design Boat

- Combine DataSpeaks with randomized experimental control *exercised over time* for *individuals*
- Tactical win now for drug rescue and repurposing
- Potential to become new gold standard for many RCTs when drugs are developed and used to manage or control chronic health disorders
- Use Ultra RCT designs and DataSpeaks’ Software as a Service (SaaS) to measure benefit and harm over time and across response variables for each individual
- <u>Estimate 10% of the cost and 50% faster and 1000 times safer !!!</u>

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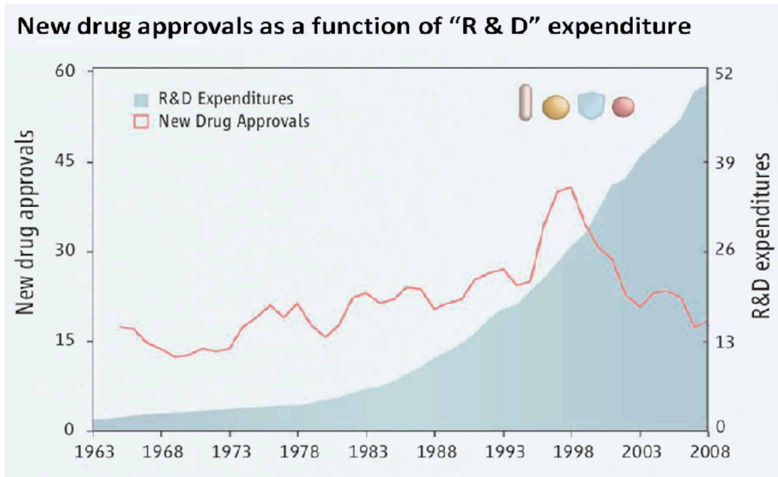
First-generation RCT designs are the current gold standard for assessing causality in drug development, drug regulation, and evidence-based medicine. Mounting evidence suggests that these represent a failing scientific paradigm.

“Houston, we have a problem”



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This is how Science Magazine portrayed part of the problem.

Houston, we have another problem

- Drug safety problem
  - About 100,000 deaths and 2,000,000 hospitalizations per year in U.S.
  - Vioxx, Bextra – product withdrawals
  - Multi billion dollar legal liability due largely to safety problems that derive from weak science that leaves room for error and bad behavior
  - Pfizer➔NCRC

Diagnose *Scientific* Causes of RCT Design Problem

- Current first-generation RCT designs, which are for *causality assessment,* date back to the 1940s
  - Streptomycin
  - ENIAC
- Four types of confounding
  - Individuality with measurement error
  - True responders with placebo responders
  - Dose with type of treatment
  - Treatment effects with how they are valued
- Too much data is going to waste

ENIAC = Electronic Numerical Integrator And Computer, the first general purpose electronic computer
Bayesian statistics are not up to solving these problems.

Elephants in the RCT Design Room

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- Why genotype patients in RCTs that wash out the effects of individual differences by design?
- Why test particular patients with only one dose or placebo when we often need to target different doses to different patients?
- Why separate clinical safety and effectiveness evaluations when these need to be balanced against each other starting at the level of individual patients?
- Why confound true responders to active treatment with responders on active treatment that would have responded to placebo?
- Epidemiology spends much effort trying to overcome confounding. Why design RCTs to confound individual differences with measurement error, doses with types of treatment, treatment effects with how they are valued, and true responders with placebo responders?

Ultra RCT Example, Mock Data

Patient Variable	Week																Interaction score	Direction[1]	Benefit/ Harm Score	Weight[2]	Overall Benefit/ Harm Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16					
	Pair 1				*Pair 2*				*Pair 3*				*Pair 4*								
	Period				*Period*				*Period*				*Period*								
	1		2		1		2		1		2		1		2						
Patient 1																					
Dose	20	20	40	40	0	0	40	40	40	40	20	20	80	80	40	40					
DBP[3]	96	98	85	81	91	96	84	87	80	78	93	98	82	77	81	78	-8.92	-	**8.92**	4	
ED[4]	3	2	2	3	2	1	2	1	3	2	1	2	3	2	2	2	0.74	-	**-0.74**	2	
Energy	4	3	4	5	4	3	4	3	2	4	3	3	4	4	2	3	1.46	+	**1.46**	2	**4.64**
Patient 2																					
Dose	0	0	20	20	40	40	0	0	20	20	80	80	80	80	40	40					
DBP	98	91	89	88	89	84	96	98	89	93	86	80	76	75	80	92	-8.56	-	**8.56**	4	
ED[4]	2	1	2	2	3	2	1	2	2	3	2	4	4	3	4	2	5.93	+	**5.93**	1	
Energy	2	3	2	2	3	1	2	3	2	2	3	3	4	3	2	3	3.05	+	**3.05**	2	**6.61**
Patient 3																					
Dose	40	40	20	20	0	0	80	80	20	20	40	40	20	20	80	80					
DBP	76	79	74	80	88	90	78	68	75	77	81	78	73	79	76	82	-7.81	-	**7.81**	4	
ED[4]	1	3	2	2	1	1	2	4	2	2	2	1	3	2	3	5	5.04	-	**-5.04**	1	
Energy	4	3	2	2	3	4	3	2	5	3	4	3	4	4	1	2	-2.67	+	**-2.67**	1	**3.92**
Group Average																					**5.06 t=6.29 p=.0242**

➢ This slide shows data and benefit and harm scores for three patients. This is an **Ultra RCT design** with **four doses** including placebo and **three dependent** or **response variables** for each of three patients.

➢ This slide illustrates use of two distinct and often complementary quantitative methods, DataSpeaks and statistics. Which method was used to describe the group and make an inference from the sample of patients to a population? Answer – statistics.

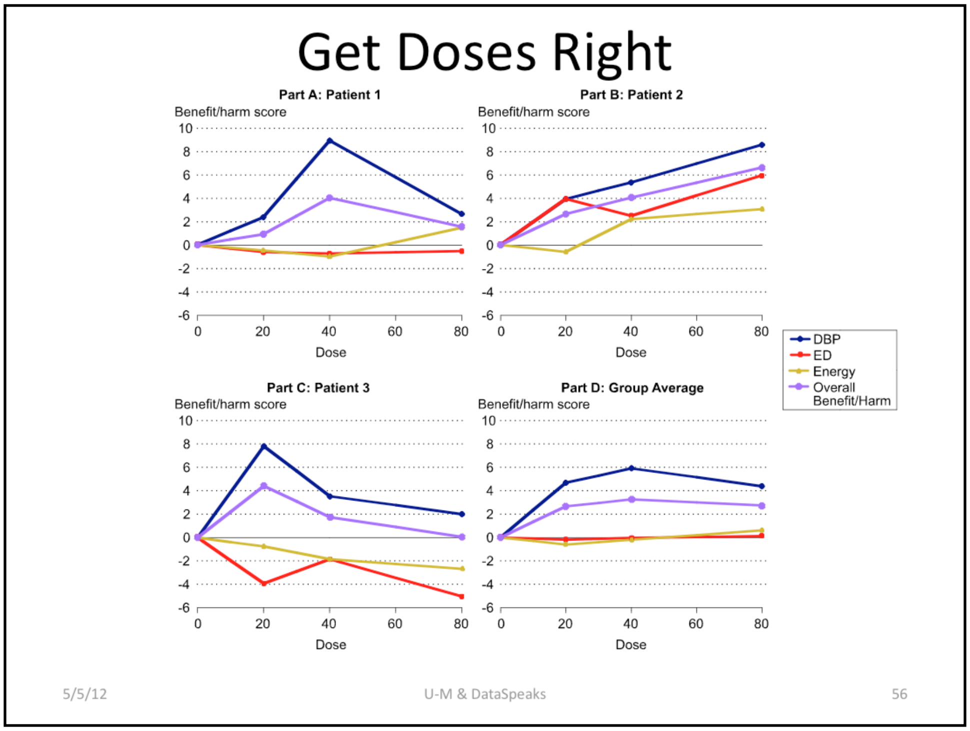
➢ Which method was used to assess causality? Answer – DataSpeaks in conjunction with randomized experimental control exercised over time for individuals.

➢ Will statisticians be willing to give up some turf with respect to causality assessment in order to advance P4 medicine, protect patient safety, help solve the translation problem, and achieve better value?

➢ Vioxx, Bextra, and torcetrapib failed because of increased risk of heart attack, stroke, and death mediated, at least in part, by increases in blood pressure (BP). See how easy it is to detect BP effects when these effects exist.

➢ Green bars for Patient 1 show that BP always was below 90 at every time when dose was 40 or more. Red bars for Patient 1 show that BP was always higher than 90 when dose was less than 40.

➢ Patient 2 shows some evidence for Delay.



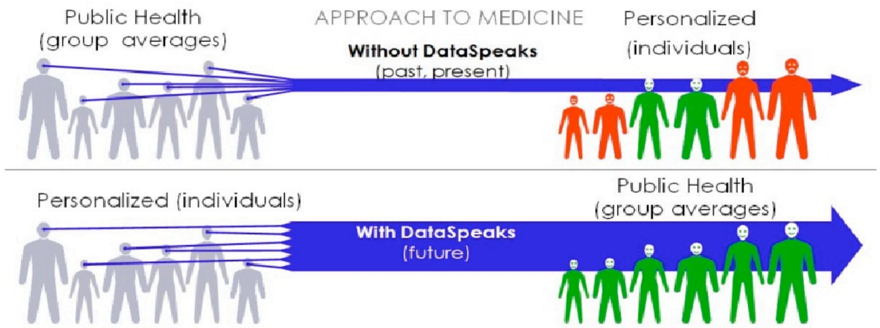
➢ This slide also shows benefit and harm as a function of dose for all three patients as well as group average results obtained with statistics.

➢ Notice that ***optimal doses*** appear to differ for these three patients and that group averaging, though often useful, tends to ***wash out*** the effects of individual differences.

➢ Such results do appear to be relevant to pharmacodynamics. Apparent treatment effects are ***measured*** directly starting at the level of individual patients that appear to be somewhat unique and have different dose requirements.

➢ The results in this slide suggest that dose response is ***not*** linear.

Harmonize P4 Medicine with Public Health Approach to Medicine



Personalized medicine that improves individual health will improve group average or public health with the help of statistics.

What problem could not be done better with multiple time series?

Forensic identification with DNA.

Most problems involving living systems, which are CDAS that manifest emergent system properties, can be done better with time series and DataSpeaks' software.

Next Steps, Collaborate?

- Publications
  - http://dataspeaks.com/resources/APA-JCCP-1992-Vol60-No2-P225-239.pdf
  - Patents
  - Need new, co-authored, peer-reviewed publication with a version of the algorithm that is
    - More mathematically elegant
    - Computationally efficient?
    - Illustrated in a particular scientific context
- Faculty and Graduate Student Projects

Next Steps, Collaborate?

- Software development
- In silico simulations as with Ultra RCTs
- J&J, tranSMART?
- Grants, e.g., SBIR
  - Phenotyping Pain Treatment Responses (NIH PhenX Project)
  - Drug Rescue by Data Rescue from RCTs
  - Diagnosing Functional Brain Disorders with a New Algorithm for Processing Functional Brain Imaging Data
- Commercialization

Thank you

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