Translational Medicine: Patterns in Response to Antidepressant Treatment and their Implications

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Rensselaer Polytechnic Institute, Troy, NY
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IEEE Schenectady Section
Sponsored by
The Engineering in Medicine & Biology Society (EBMS)

Questions

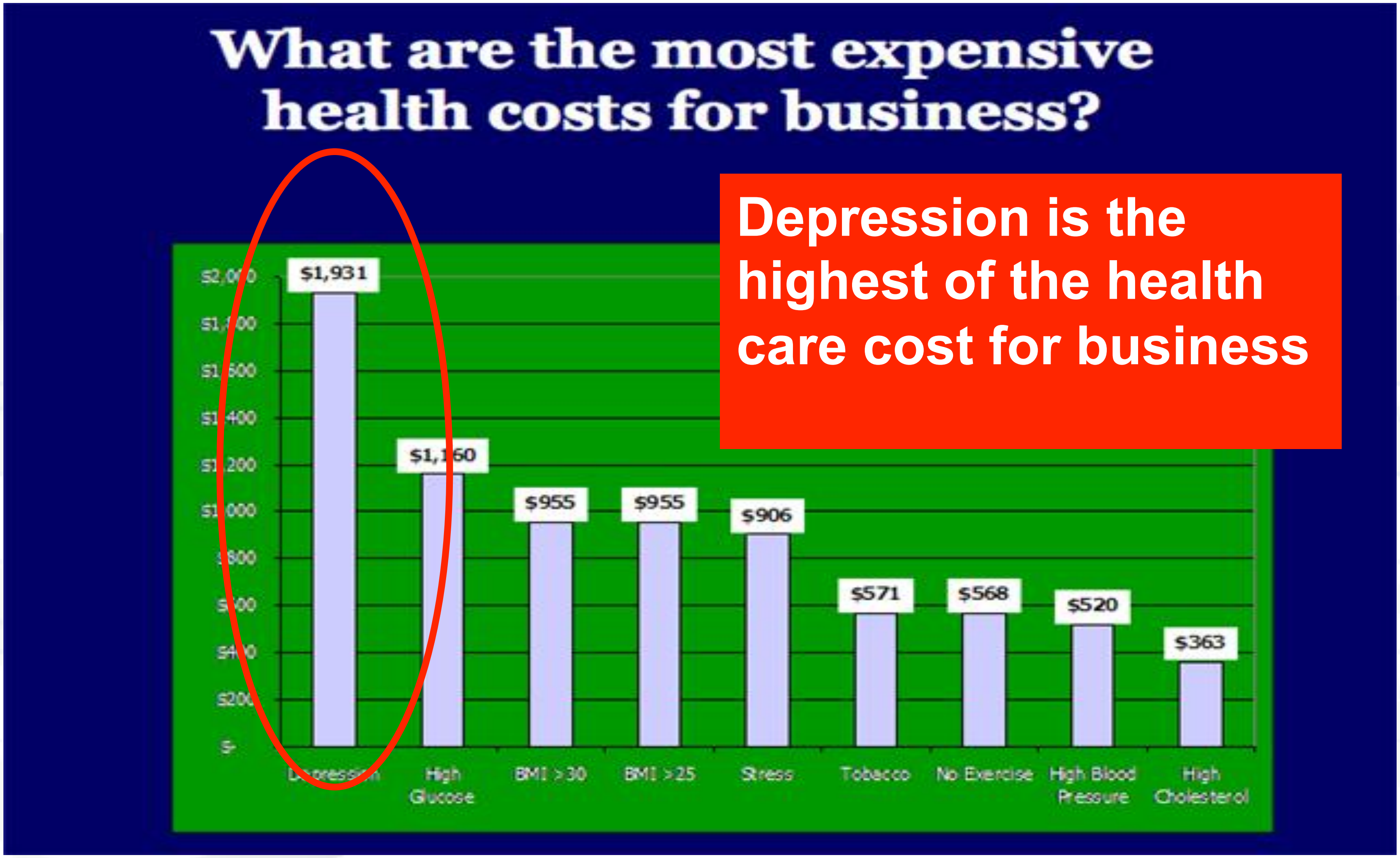
Some people on antidepressants commit suicide. Is it possible that the antidepressant drug can cause this to happen?

How can differential equations help us to understand what is going on?

Take Home Messages

- Depression is complex and personal. It requires unbiased multidisciplinary approach focused on the person.
- Depression is a global concern. The Web has global reach and needs to be explored as a resource for helping people with depression.
- Effectiveness may be the same, but patterns differ and order of symptom improvement matters.

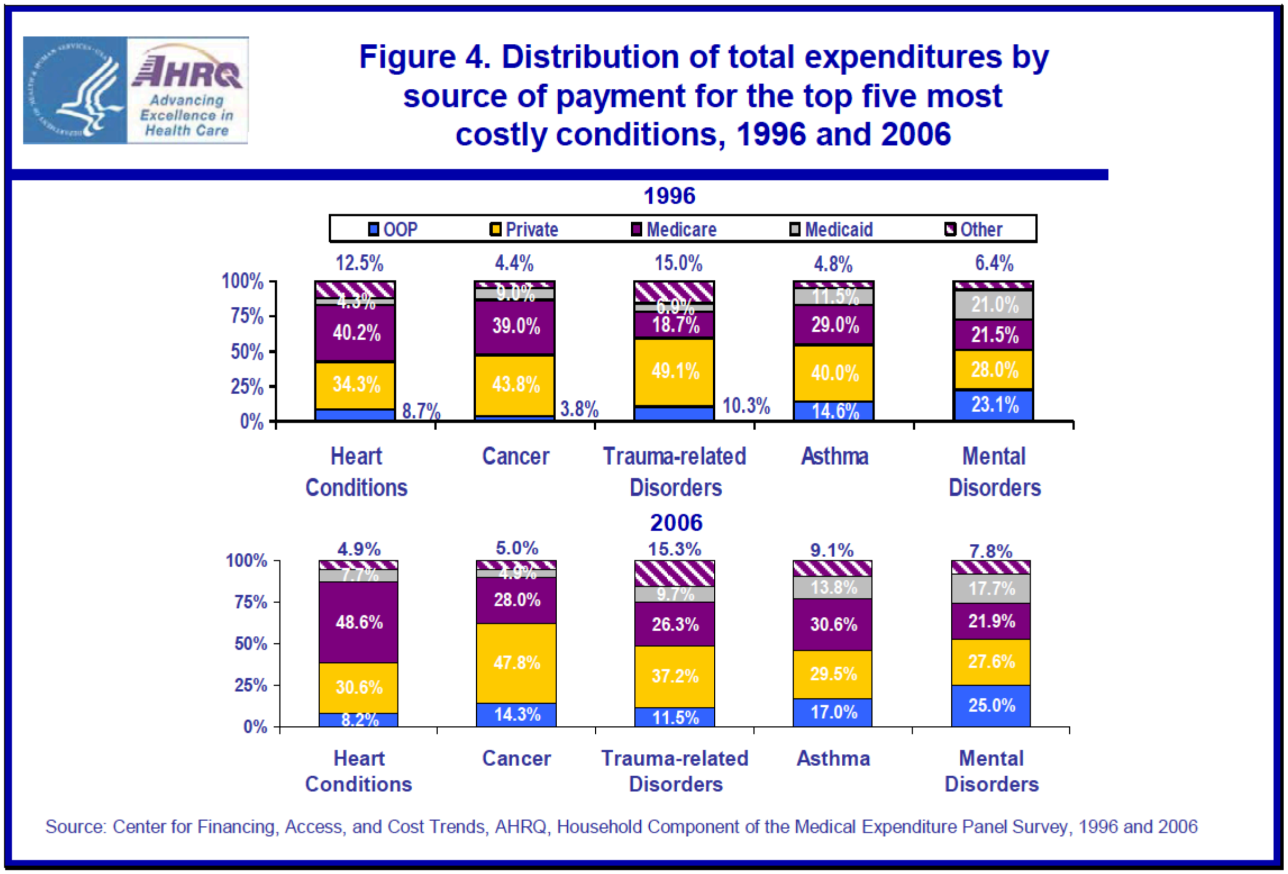
The Economic Burden



Source: The Healthy Thinking Initiative

http://www.preventingdepression.com/costs.htm

The Five Most Costly Conditions



1996 and 2006: Estimates for the U.S. Civilian Noninstitutionalized Population

http://apps.who.int/gb/ebwha/pdf_files/EB130/B130_9-en.pdf

The Global Burden of Depression

WHO's projections state that by 2020 depression with be the 2nd largest health burden worldwide,

by 2030, it will be the largest.

http://www.preventingdepression.com/costs.htm
http://www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf

What is depression?

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Moreover, depression often comes with symptoms of anxiety. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities.

At its worst, depression can lead to suicide.

Almost 1 million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day. For every person who completes a suicide, 20 or more may attempt to end his or her life (WHO, 2012)

Overview

- **Why we did this work** - to improve quality of life for millions of people suffering from depression
- **How we did it** - used differential equations ("neural network") to model and compare response to different antidepressant treatments
- **What we found** - different response patterns for the two treatments - the order and timing of improvement of symptoms were different
- **What we think it means** - improvement in selection of treatment thereby reducing unnecessary costs and suffering. Potentially saving lives

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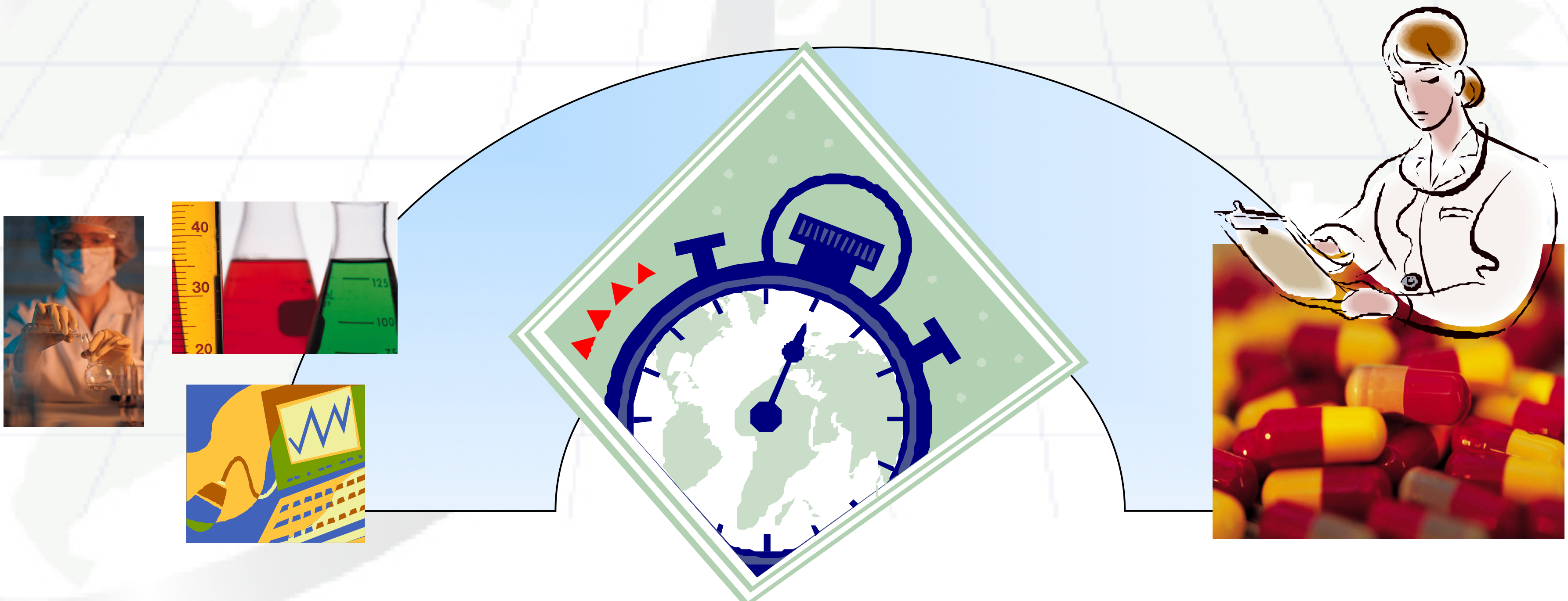
Translational Medicine

- Rapid transformation of laboratory findings into clinically focused applications
- ‘From bench to bedside and back’
    - “and back” includes patients!



HUGE PROBLEM

Characterized by persistent and pathological sadness, dejection, and melancholy

Prevalence (US)

6% year (18 million)

16% experience it in their lifetime

Cost

44 Billion (1990)

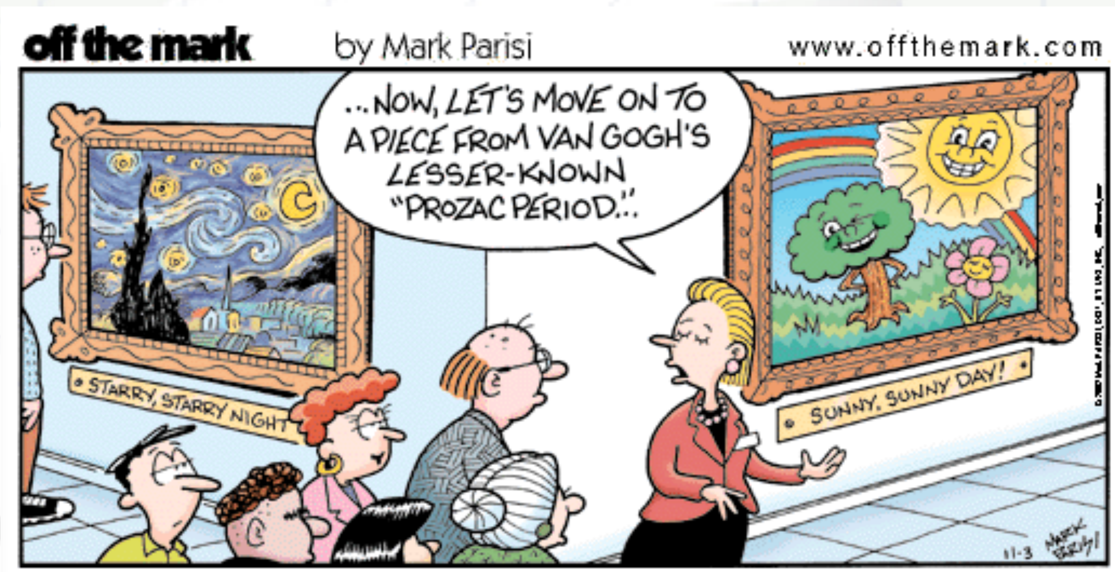
Impact

1% Improvement means (180, 000 people helped)

1% Improvement means (440 million in savings)

Widespread

"As you can see, the antidepressants are doing great!"



EEYORE WHEN HE REMEMBERS HIS PROZAC

Treatment Choice Vague

No easy answer

MAJOR RECOMMENDATIONS

Recommendations are identified as either "evidence-based (A-D, I)" or "consensus-based." For definitions of the levels of recommendations see the end of the "Major Recommendations" field.

I. **First-Line Treatment Of Major Depressive Disorder (MDD)**

For patients with mild to moderate Major Depressive Disorder (MDD), use either antidepressant medication or psychotherapy[1] as first-line treatment.
Evidence-based

Given the lack of evidence on a clearly superior approach for mild to moderate MDD, treatment decisions should be based on patient and clinician preference, potential side effects, and cost.
Consensus-based

For patients with severe or chronic MDD, combined treatment with antidepressants and psychotherapy[1] is recommended as first-line treatment.
Evidence-based

If antidepressants are to be used, any class of antidepressant (selective serotonin reuptake inhibitor [SSRI], tricyclic antidepressant [TCA], serotonin norepinephrine reuptake inhibitor [SNRI], norepinephrine reuptake inhibitor [NRI], or dopamine agonist [DA]) can be prescribed as first-line treatment of MDD.
Evidence-based

Given the equivalence of therapeutic effect, base the choice of antidepressant on patient's prior response, patient and clinician preference, potential side effects, and cost.
Consensus-based

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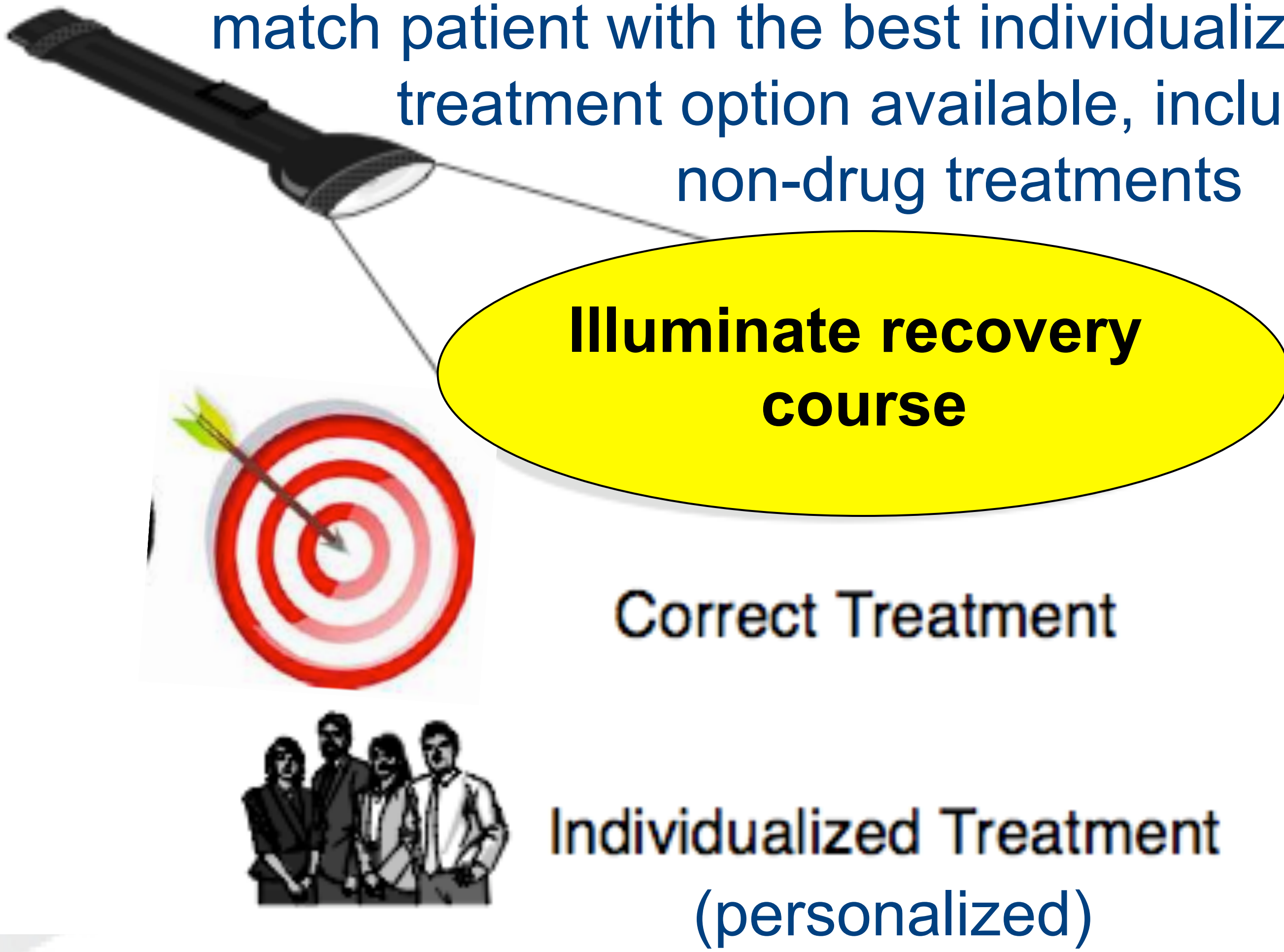
Research Goals

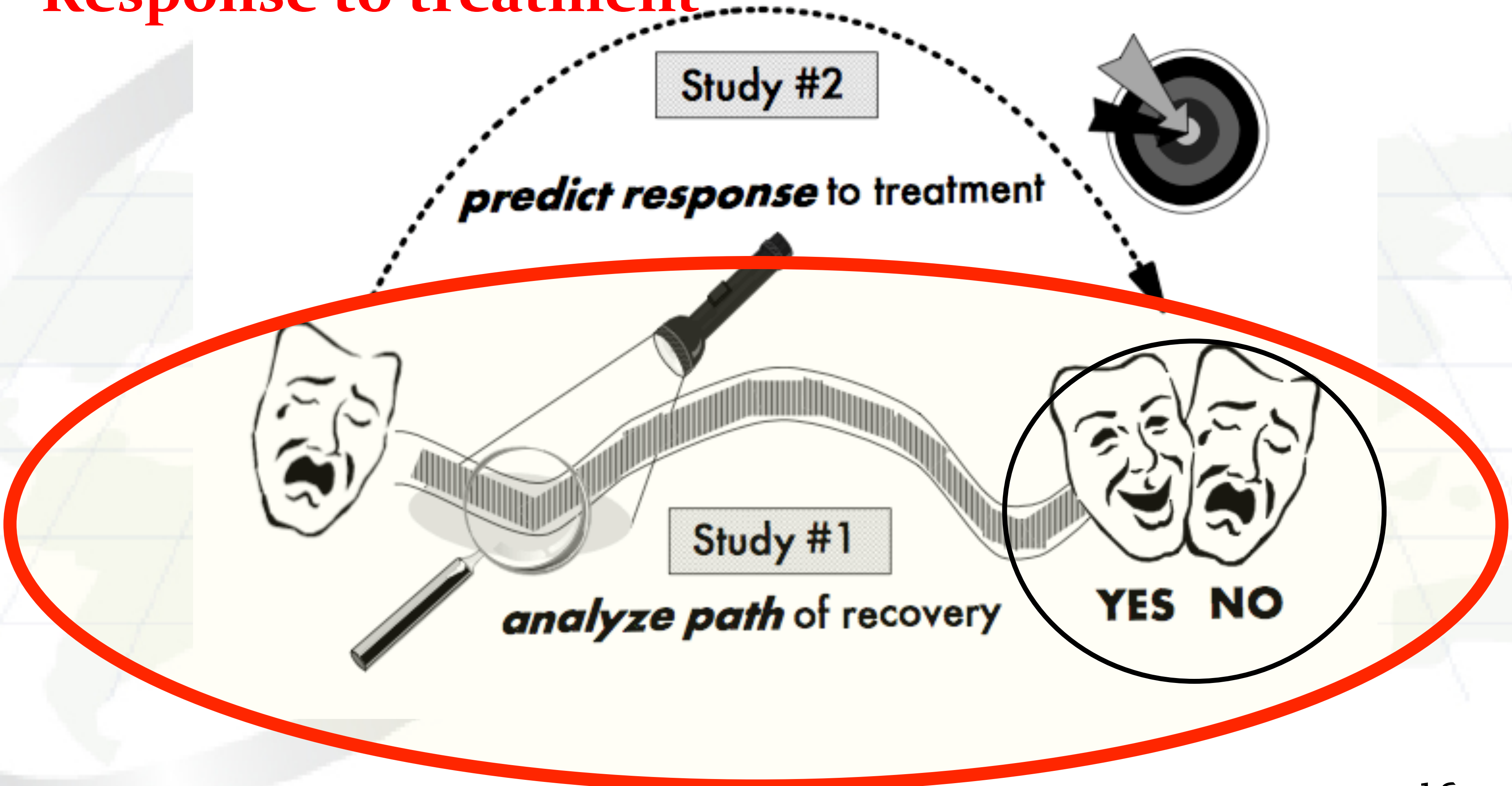
Properly diagnose and properly match patient with the best individualized treatment option available, including non-drug treatments



Treatment Response Study

Today's talk focuses on:

Response to treatment



Depression Background

- Clinical Depression
- Treatment
- Symptom Measurement
- No specific diagnosis
- No specific treatment

Clinical Data

Symptoms

-HDRS (0-4 scale)

Treatment

-Desipramine (DMI)

-Cognitive Behavioral Therapy (CBT)

Outcome

- Responders

Hamilton Psychiatric Scale for Depression

Clinical Instrument standard measure in clinical trials.
Example of first three items of 21 items that measure individual Symptom intensity.

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)

____

0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT

____

0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

____

0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

Why Model?

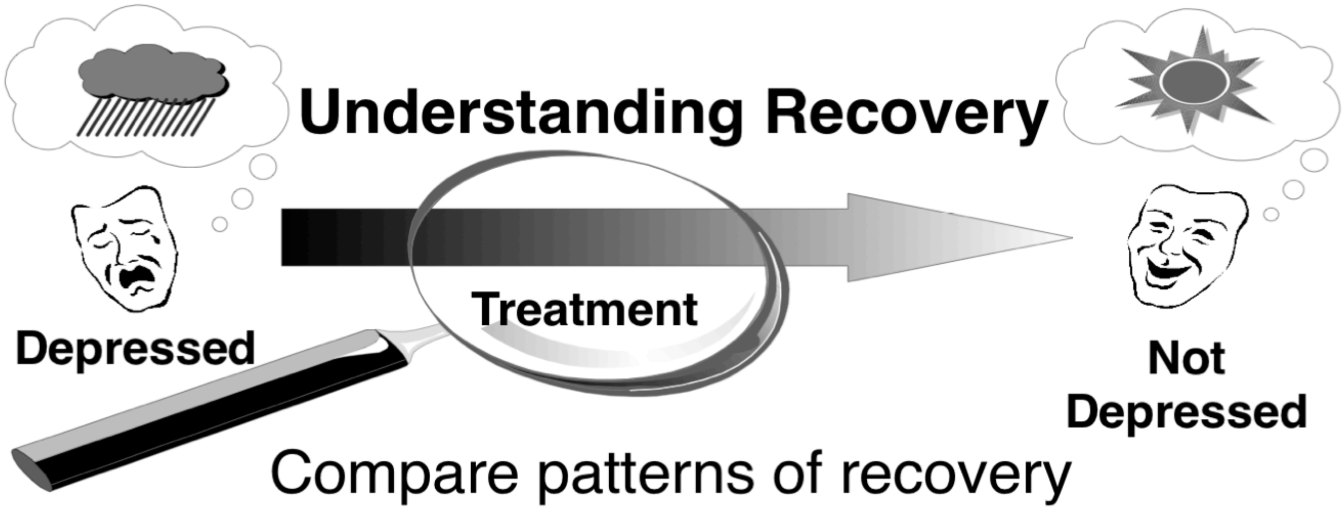
Recasting the problem into mathematical terms makes it:

Easier to understand

Easier to manipulate

Easier to analyze

Understanding Recovery



Compare patterns of recovery

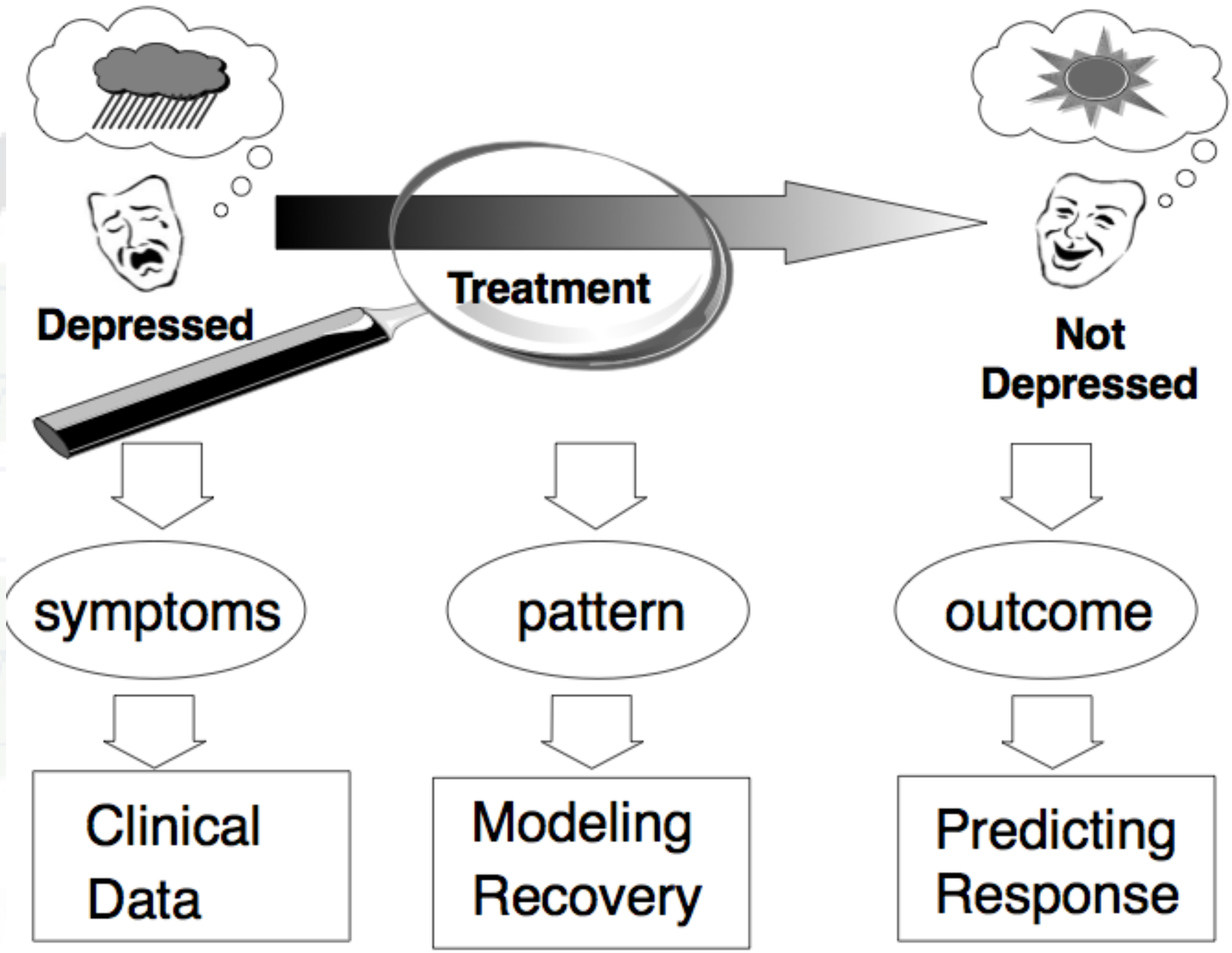
6 week	**When response begins**	**(Latency)**	Δt
7 symptoms	**Indirect (between symptoms)**	**(Interaction Effects)**	w
2 treatments	**Direct (on symptoms)**	**(Treatment Effects)**	u,v

Recast as dynamical system

Patient	**Recovery pattern**	**(Differential Equations)**	$\dot{x}$

1

Understanding Recovery



Depression Data

7 Symptom Factors

	Physical:	E Sleep
		M, L Sleep
		Energy
	Performance:	Work & Interests
	Psychological:	Mood
		Cognitions
		Anxiety

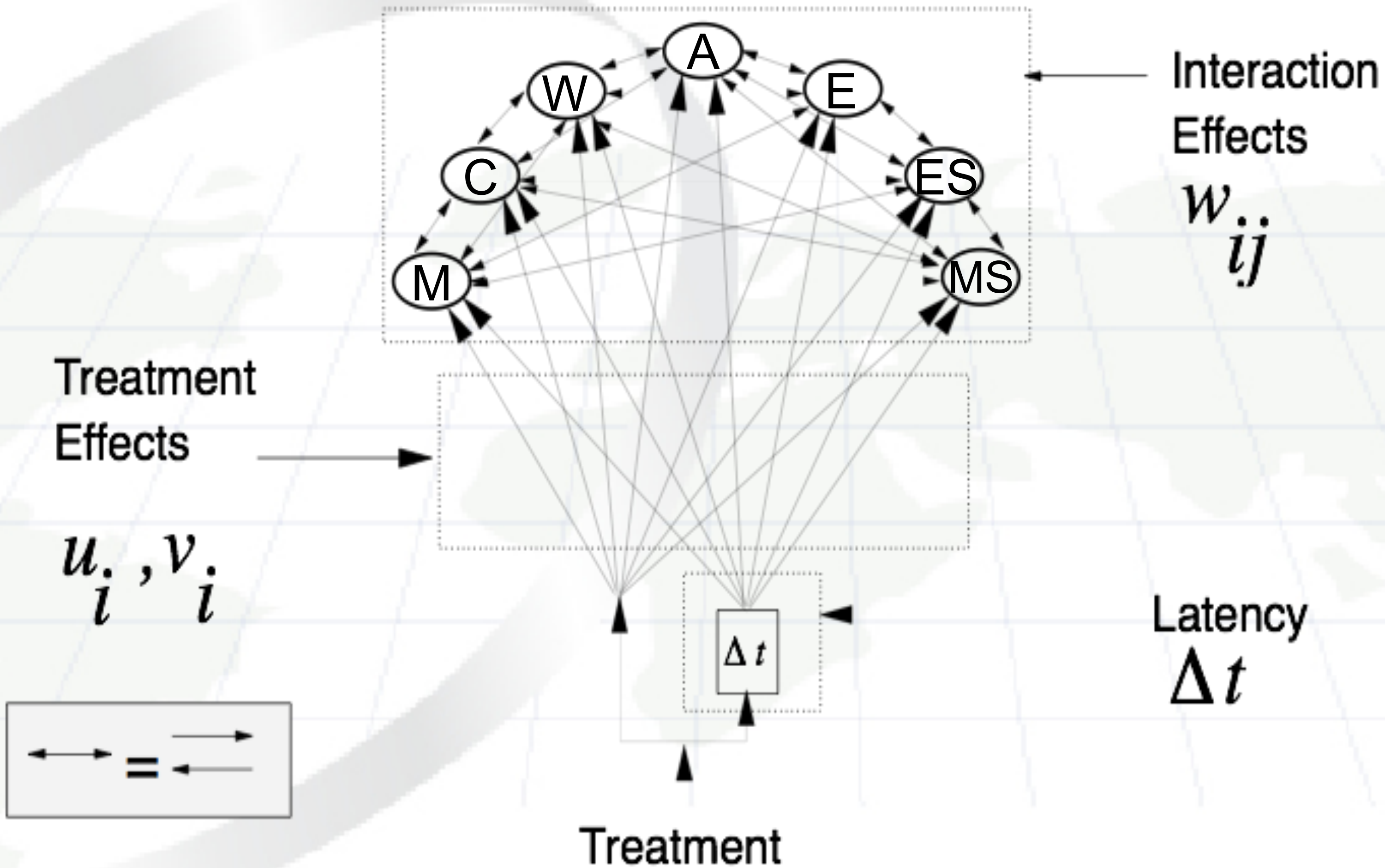
2 Treatments

Cognitive Behavioural Therapy (CBT)
Desipramine (DMI)

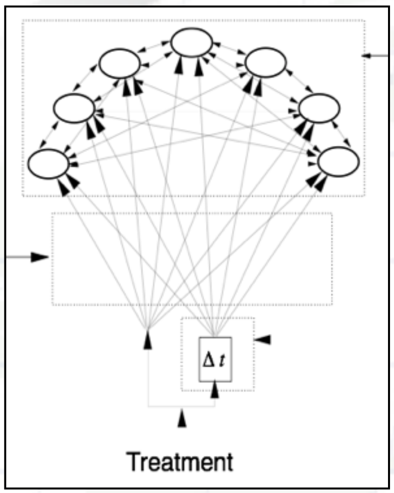
Clinical Data

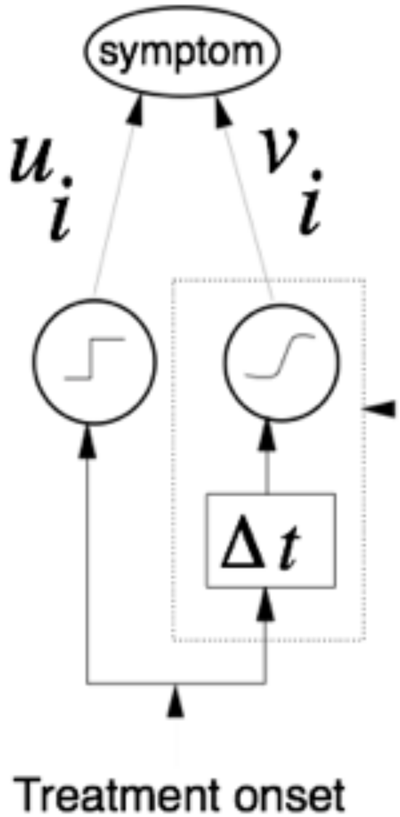
Responders = improvement >= 50% on HDRS total
N = 6 patient each study
6 weeks = 252 data points (converted to daily)
each study (CBT and DMI)

Overview
Recovery Model and Parameters



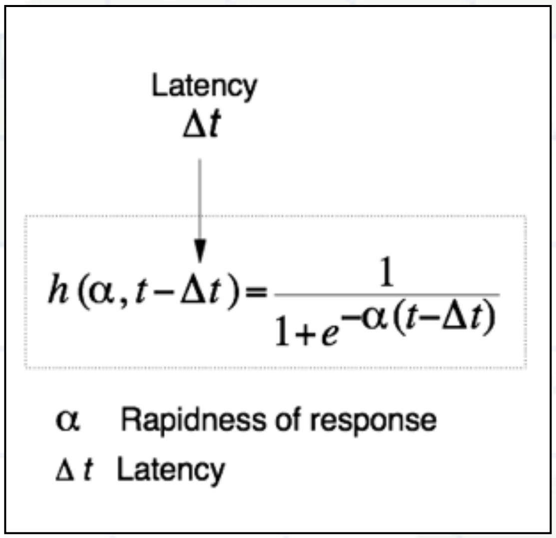
Modelling
Time to Response



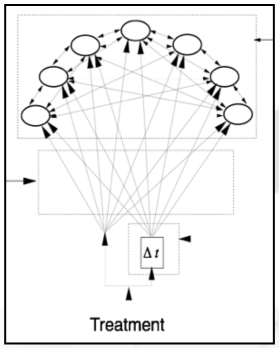


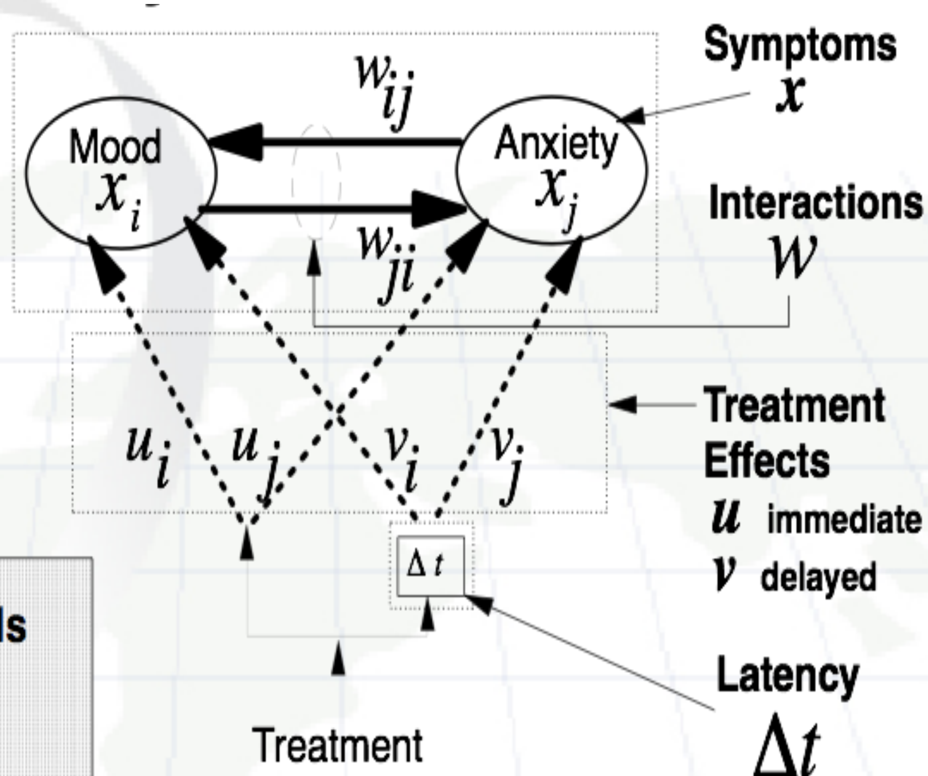
Latency

Δt



Modelling Treatment Effects





2 Models
- CBT
- DMI

Optimized parameters specify model
Initial conditions predict patient trajectory

Recovery Equation (Luciano Model)

$$\ddot{x}_i = -A_i \dot{x}_i + \sum_{j=1}^{7} (x_j - B_j)\, w_{ij} + s(t)\, u_i + h(\alpha, t - \Delta t)\, v_i$$

Acceleration of symptom

Stabilizing factor

Rate of symptom change

7 symptoms

Symptom

Baseline

Interactions
between symptoms

Immediate effect
step function

Treatment Effects
on each symptom (strength)

Delayed effect
sigmoid function

Steepness

Latency

Training the model

estimated

$$L = \int_0^T \sum_{ik} \left(\left(X_{ik} - \hat{X}_{ik} \right)^2 + \mu_{ik} \left(\dot{\hat{X}}_{ik} - f\left(\hat{X}_{ik} \right) \right) \right) dt + K \sum_j P_j^2$$

actual

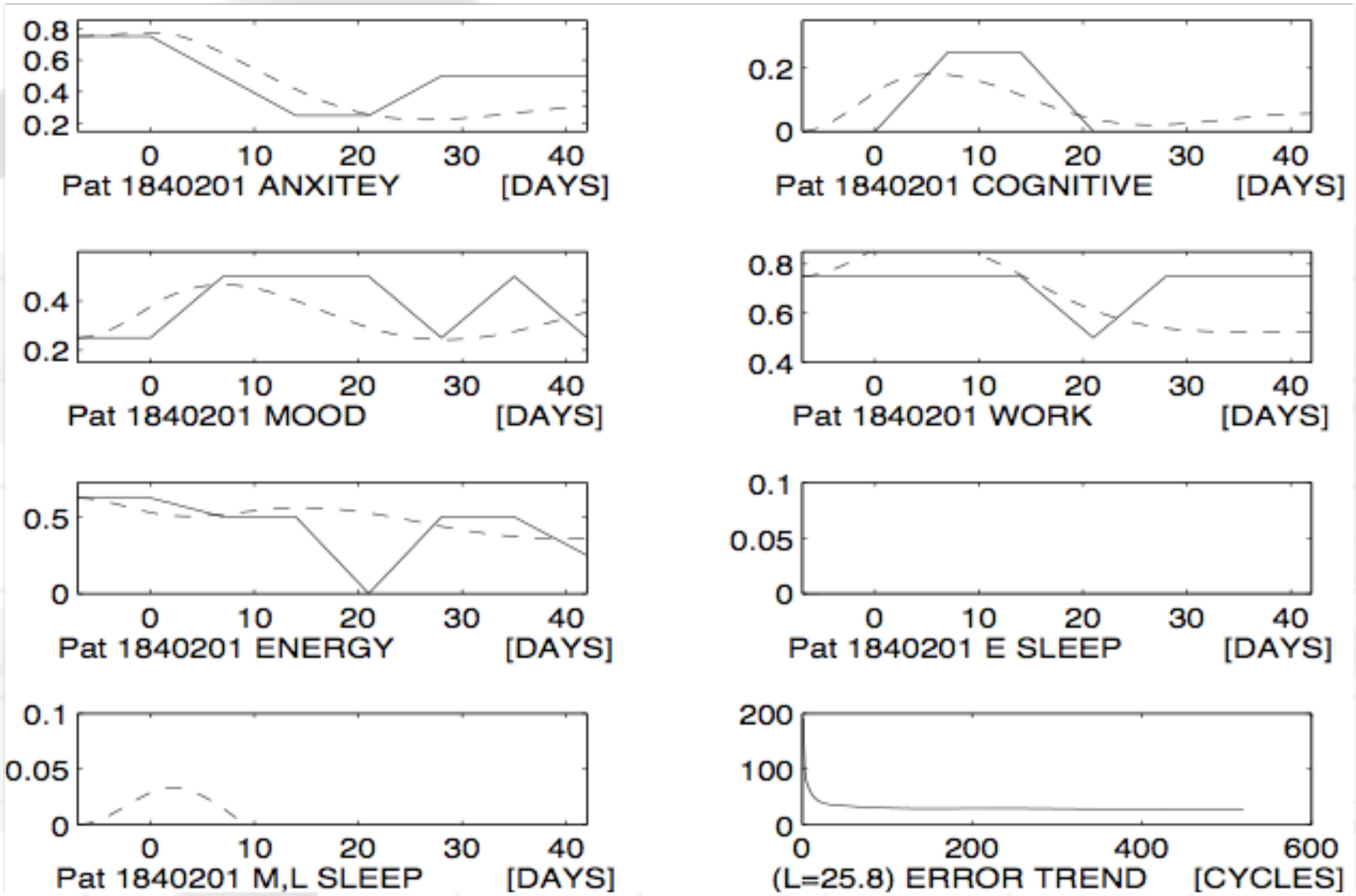
L = Error term
X = data
i = symptoms
j = parameter
k = patients

Obtain optimized parameters

- -fit patient data
- -train on time course
- -minimize error term L
- -gradient descent on parameters

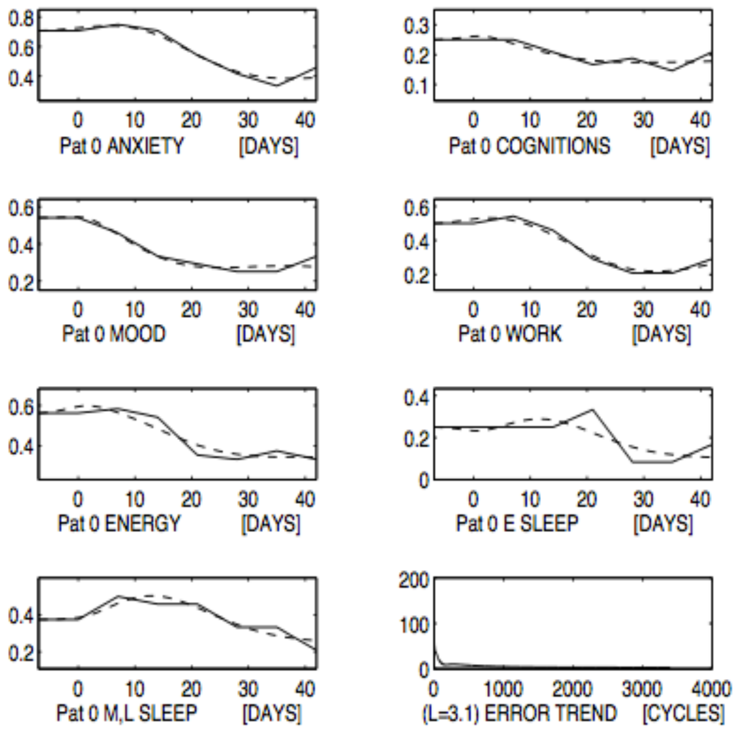
Example Patient (CBT)

Individual Patient Recovery Pattern and Error



Fit of Model on for individual patient captures trends but not entire pattern. Not good enough.

Recovery Pattern and Error



(a) Predicted and actual mean patterns of recovery (CBT)

Model on data for patient treatment group captures entire pattern. Good fit of Model to data.

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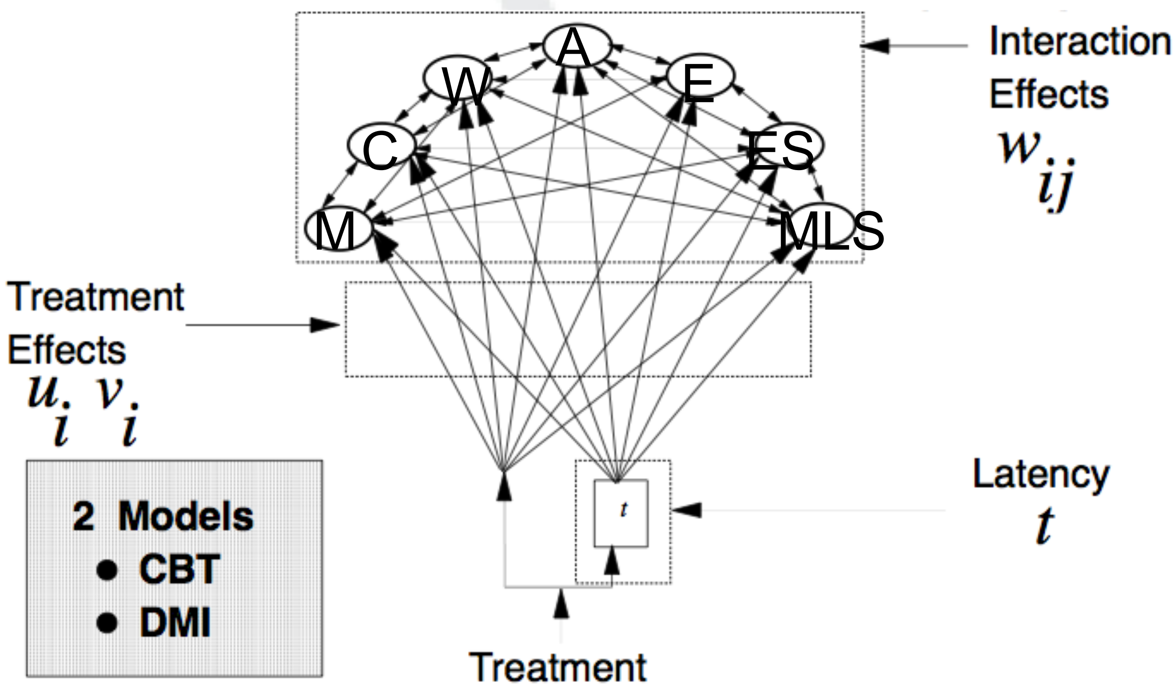
- **What we found - different response patterns for the two treatments - the order and timing of improvement of symptoms were different**
- What we think it means - improvement in selection of treatment - less trial and error

Results

Optimized parameters specify model

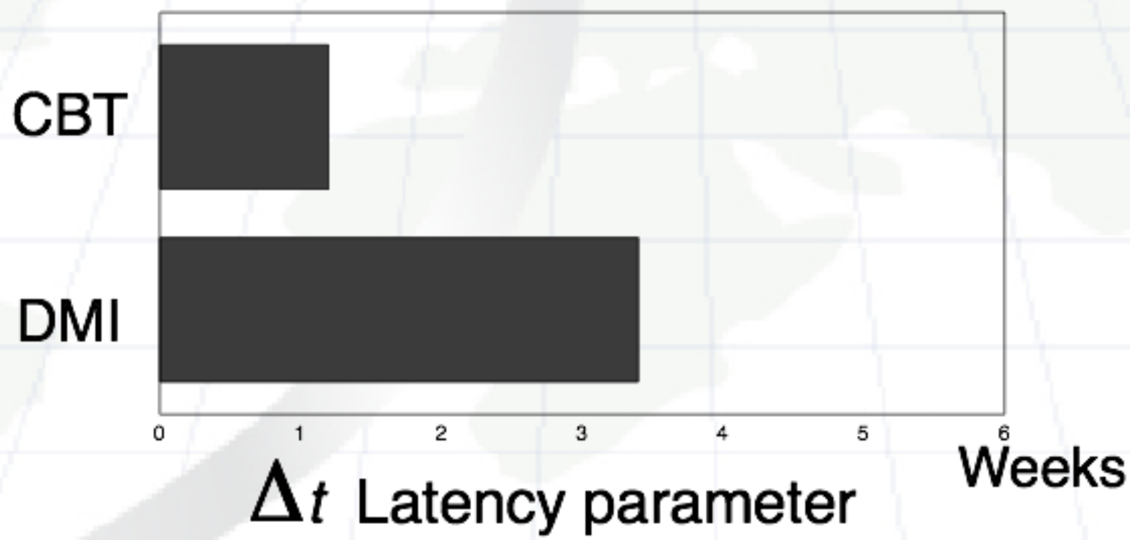
Initial conditions predict pattern trajectory



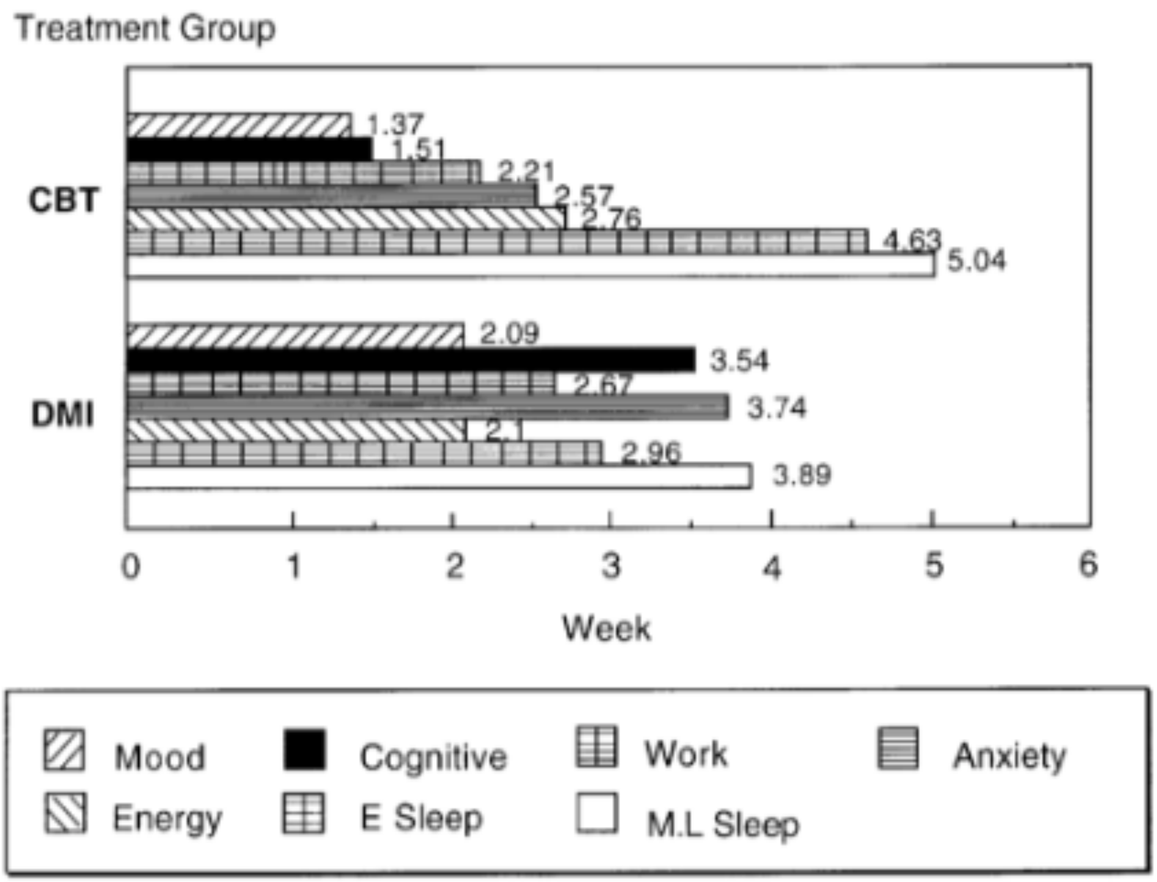
Latency

Δt = response delay

CBT: 1.2 weeks
DMI: 3.4 weeks



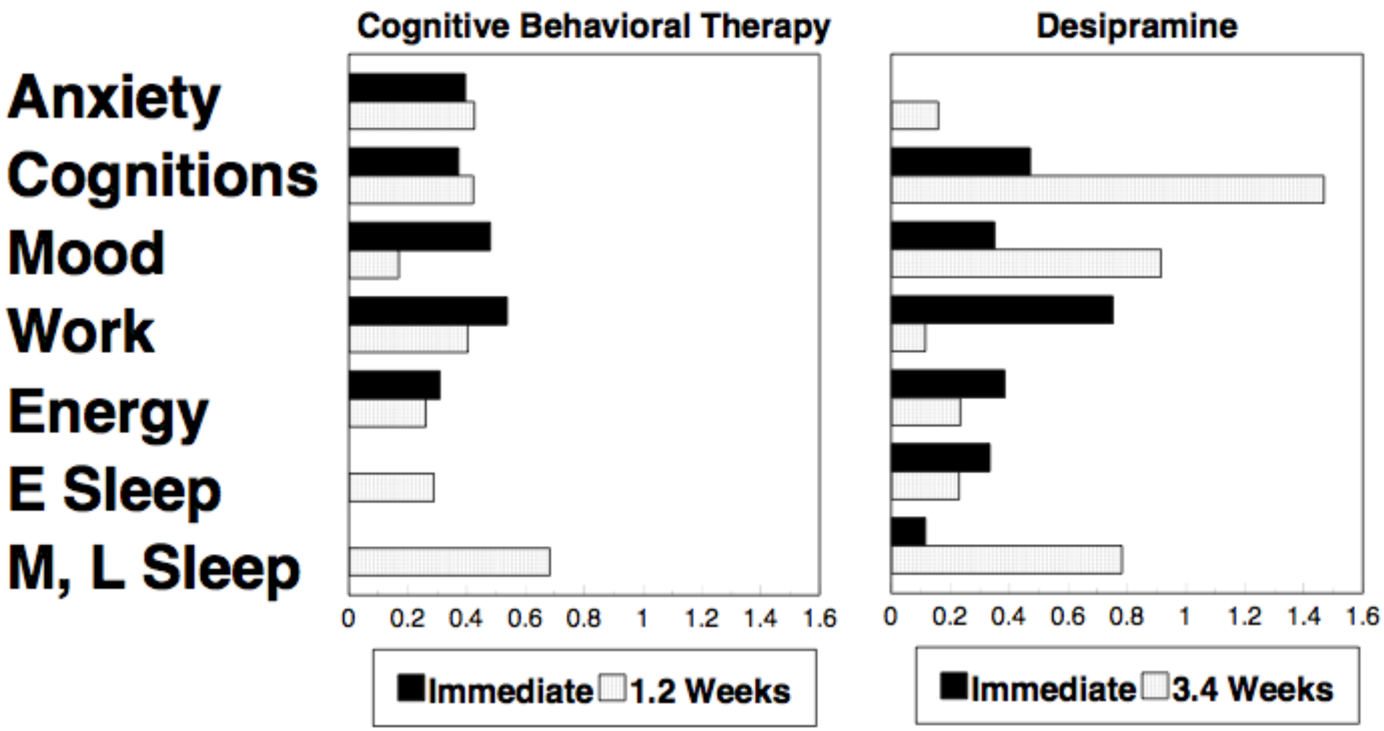
Mean ½ Reduction Time



CBT varies 3.7 wks

DMI varies 1.8 wks

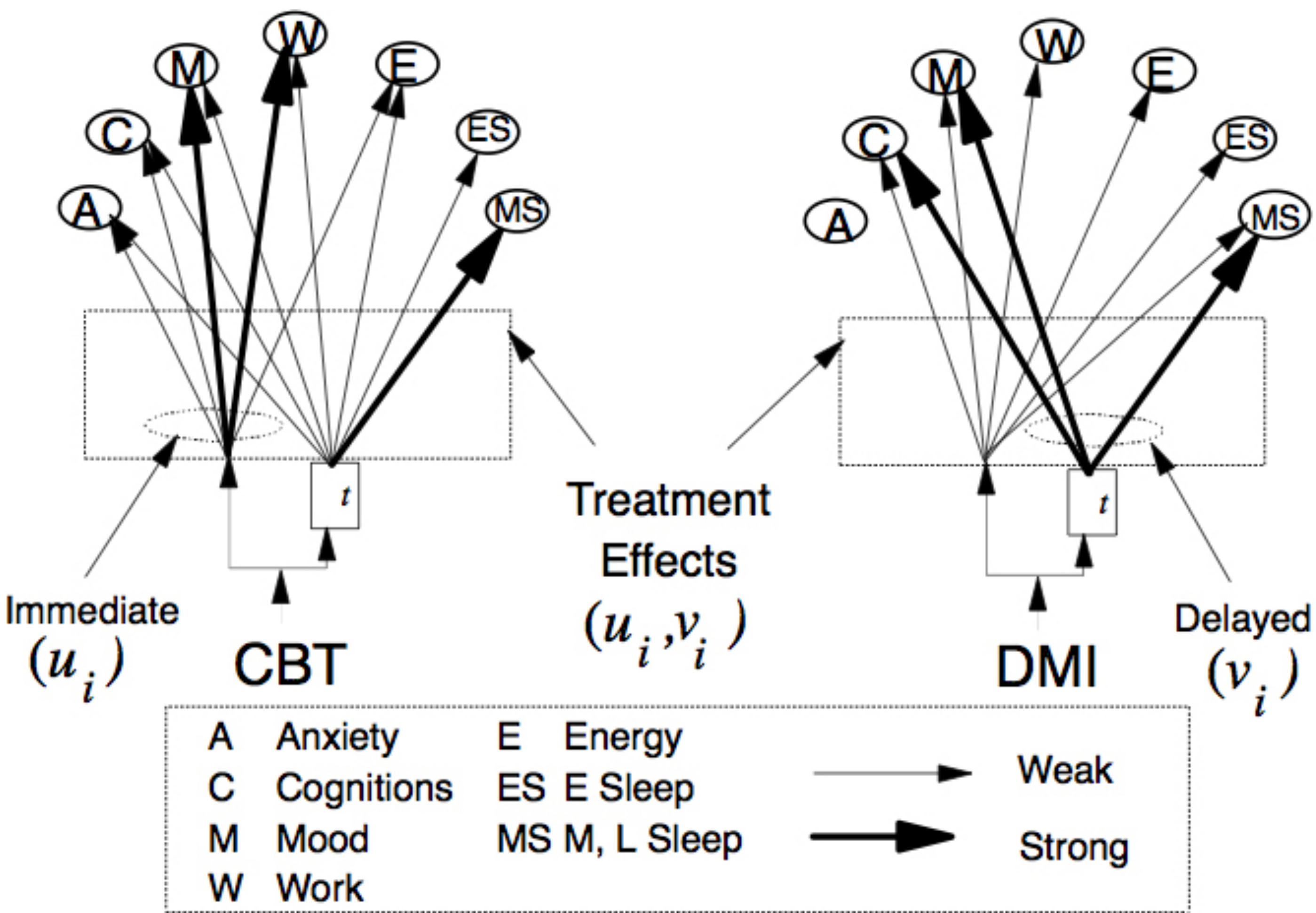
Direct Effect of Treatment



coefficients (strength)

Immediate (u_i) vs. Delayed (v_i)

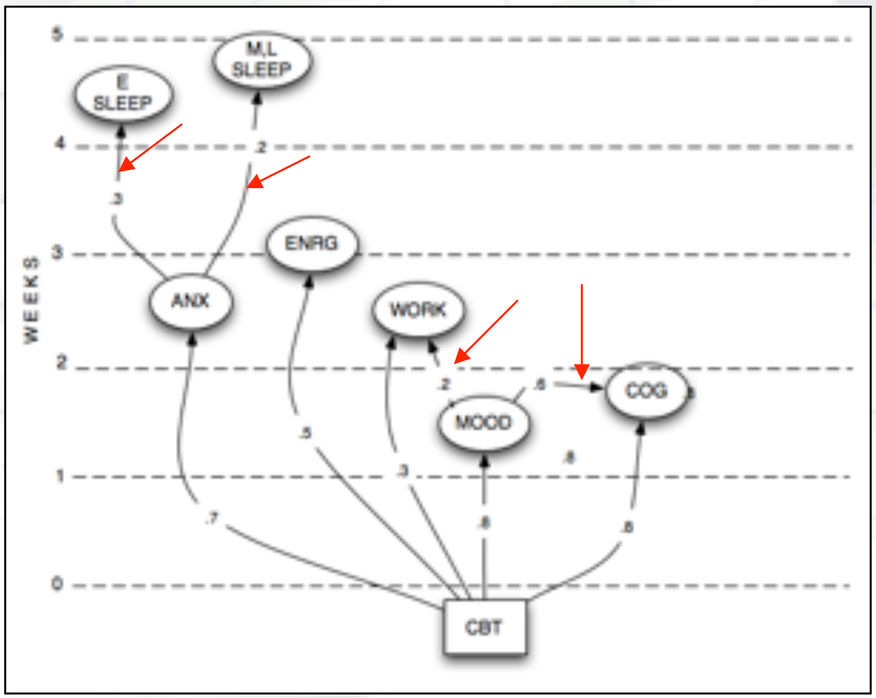
Direct Treatment Intervention Effect



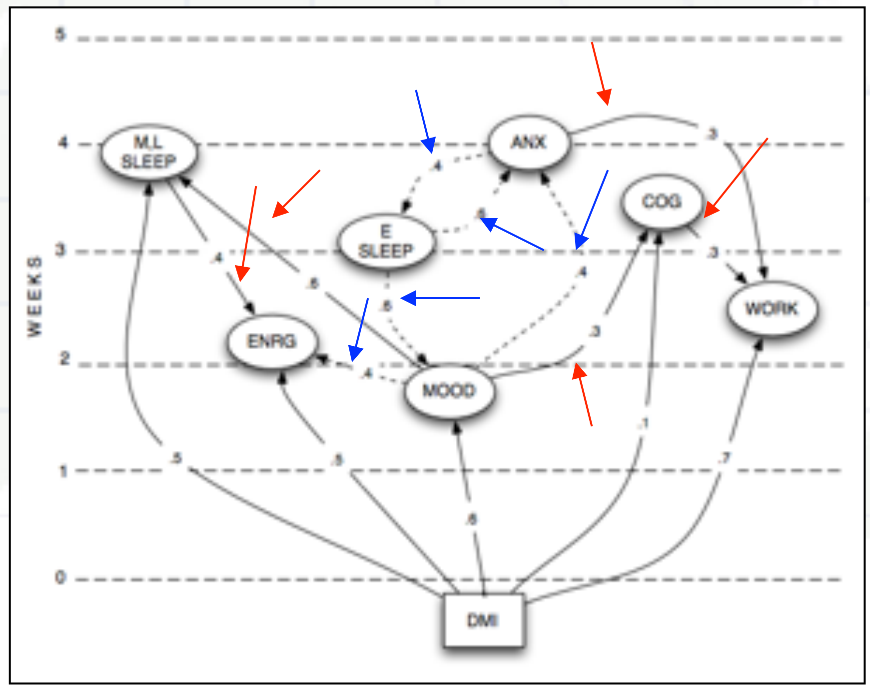
Treatment Effects and Interaction Effects

DMI:
- **Interactions > 2x**
- **Loops**

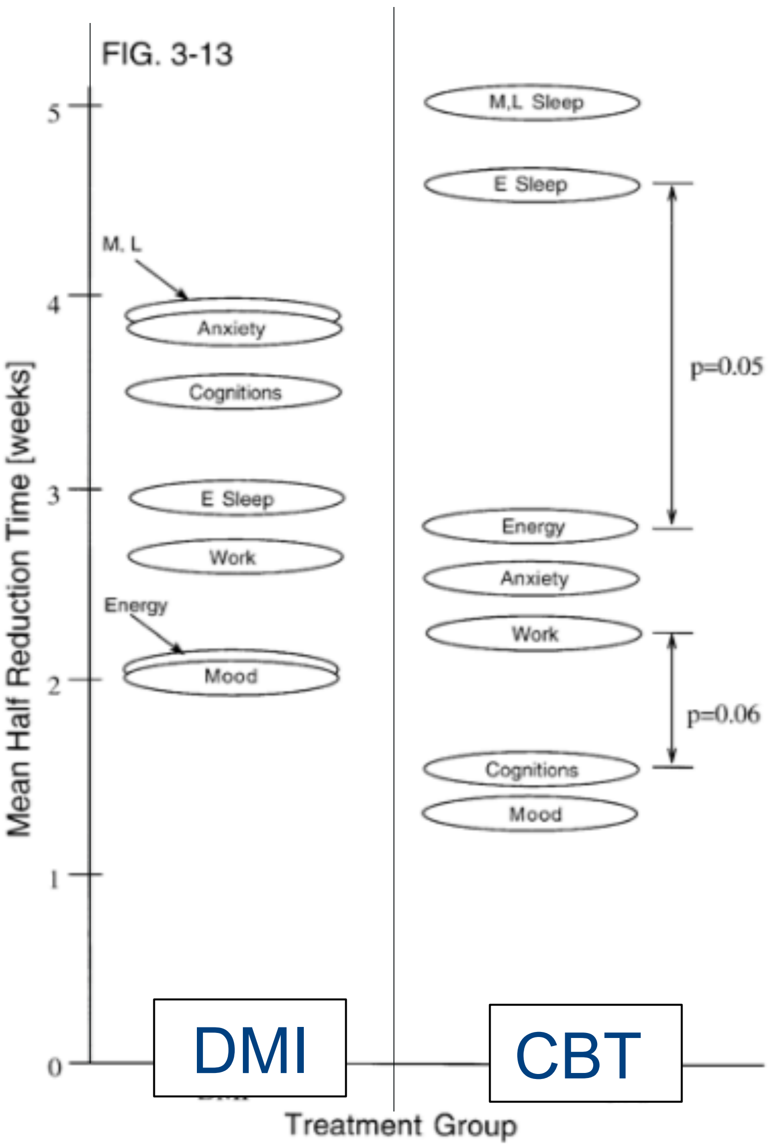
CBT
Sequential



DMI
(delayed)
CONCURRENT



Different Response Patterns for Different Treatment



Order and Time a symptom improves are both different

This is important because it shows how an antidepressant medication could lead to a suicide.

By giving a suicidal patient DMI, you could increase the patients energy before the suicidal thoughts improve. This could give them the energy to act on those suicidal thoughts.

CBT (talk: no drugs)
DMI (drug: tricyclic antidepressant)

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Conclusions

- A neural network model is capable of predicting and describing recovery patterns in depression
- We can do better than trial and error treatment protocols, which are still the norm today!

- Recovery patterns differ by treatment
  - Cognitive Behavioural Therapy is **sequential**
  - Desipramine is **concurrent (after delay)**

- Recovery patterns provide insights to patient response that can inform treatment choices

Limitations

Model:

- Assumes symptoms interact
- Assumes treatment acts directly
- Permanent vs. transient
- Causal vs. sequential
- Statistical fluctuations not handled

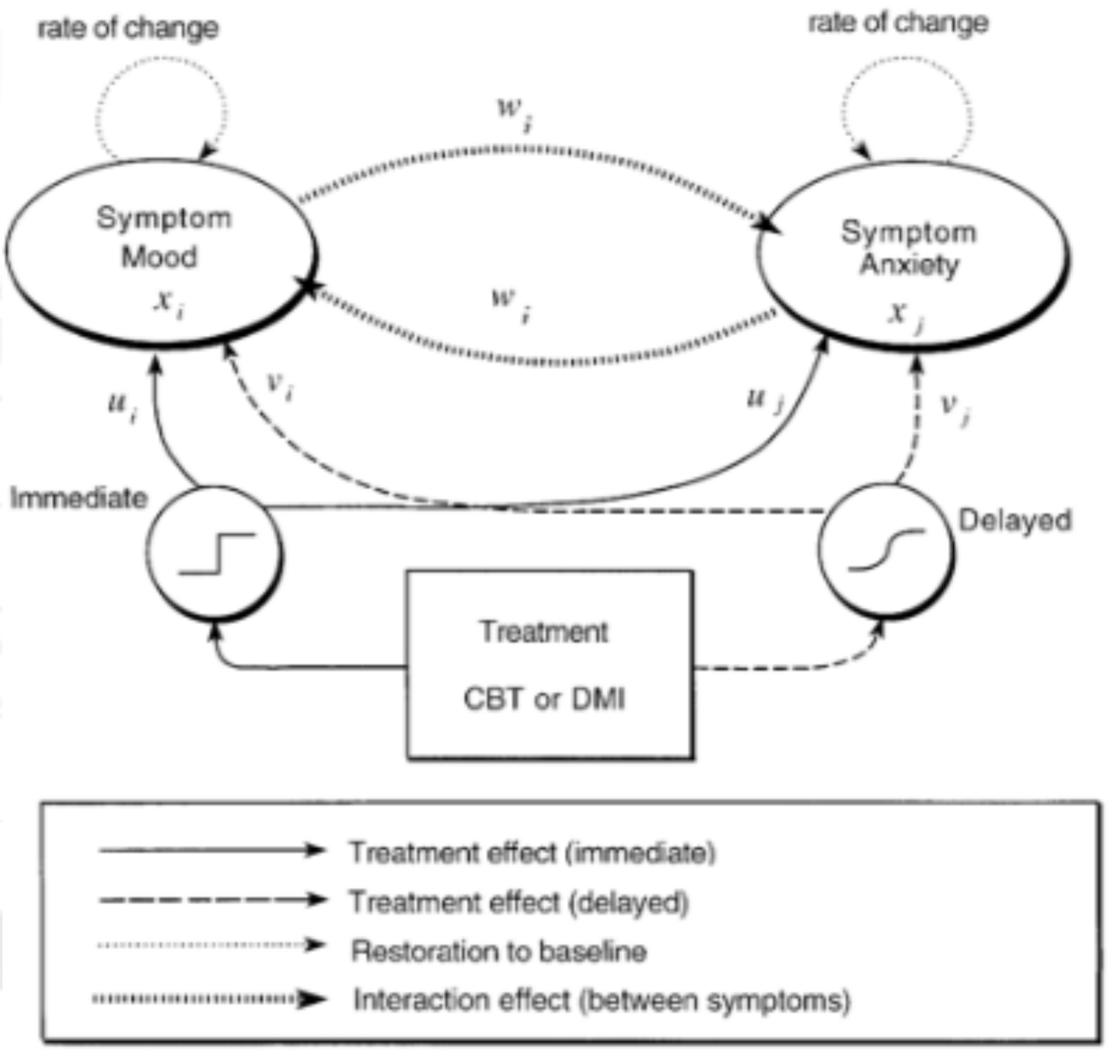
Study:

- CBT measurement intervals vary
- Small sample size
- Initial 6 weeks of CBT (entire=16)
- Finer resolution of measurements (2-3/day)

Thank you!

Backup Slides

Recovery Model
(detail)



Consistent with earlier studies

- Quitkin, 1984, 1987

  Persistent improvement after delay

- Katz, 1987

  Mood and cognitive impairment at 1 week predicts response
  Retardation improves much later*

- Nagayama 1991

  Severity at 1 week predicts response

- Bowden 1993

  Mood at 3 weeks predicts response for fluoxetine (Prozac)

*some discrepancies with our patient data

Summary

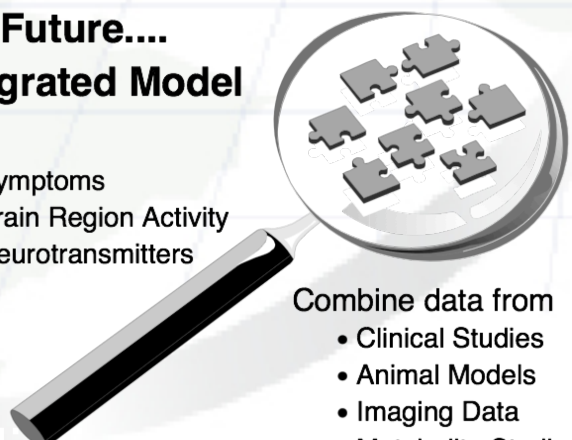
- Neural network methods applied to clinical research in depression
- Useful to understanding recovery dynamics
- More powerful than current methods used for clinical depression research

Conclusions

- BP (nonlinear method) consistently outperformed MR (linear method)
- Still, the prediction was not statistically significant (F=0.0143, p=1.000)
- But, the theory implies proportion of variance for the network is
  - df/N = 27/99=27.3% for ramdom data
  - Actual was 66.7% >> 27.3%
- Suggests
  - predictive relationships are present
  - larger study with more data needed

Future....
Integrated Model

Link
- Symptoms
- Brain Region Activity
- Neurotransmitters



Combine data from
- Clinical Studies
- Animal Models
- Imaging Data
- Metabolite Studies

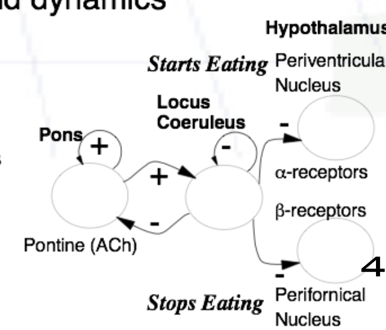
Link to the Future

Integrate knowledge about:
symptoms, brain regions, transmitter systems, pharmacological agents, and dynamics to build integrated models

symptom: appetite & weight

Two norepinephrine pathways
locus coeruleus to the hypothalamus affect feeding behavior.
One excites, the other inhibits.

DMI (presynaptic drug) induces eating prevents norepinephrine inactivation by blocking reuptake



At RPI WSRC, our observatories build and monitor new tools and processes that are needed to address the Web's complexity and multifaceted nature.

Automating Health Data

Health Web Science is an emerging subfield of Web Science which looks to understand the increasing amounts of data from the health and life science fields.

In order to advance Health Web Science, one approach is in automating health data.

RPI TWC builds tools to automate data interoperability across the web

(and therefore the world).

Department of Health and Human Services' Developer Challenge

In June 2012, HHS issued the first of its seven challenges calling for developers “to make high value health data more accessible to entrepreneurs, researchers, and policy makers in the hopes of better health outcomes for all.”

A group from RPI TWC won first place in the competition, by using semantic technologies and in-house developed software, such as csv2rdf4lod, LODSPeaKr, Farrah and DataFAQS.

HHS wanted *Liquidity*

"new designs ... that form the foundations for ... liquidity"

RPI TWC provided: 2B triples among 1M URIs
•Dataset Linked Data
◦Machine and Human views (via conneg)
◦Faceted search of datasets
•Dataset dumps (.ttl.gz)
◦For each dataset, and for *the whole thing*.
Dataset query (http://healthdata.tw.rpi.edu/sparql)

HHS wanted *Metadata*

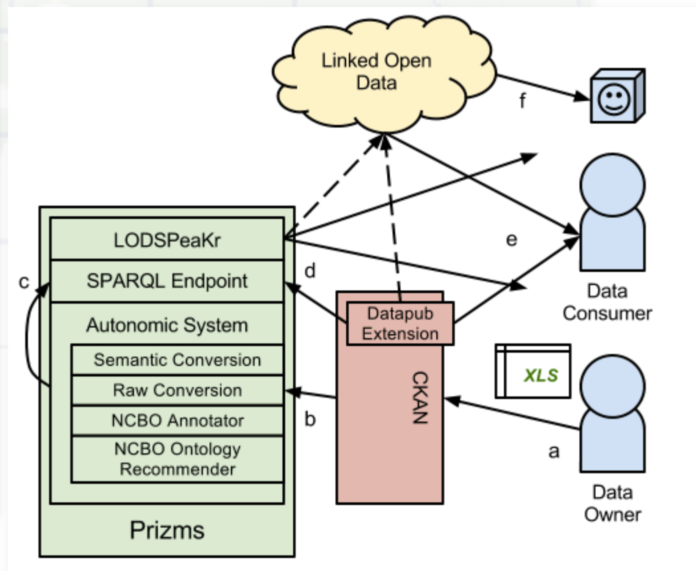
"... application of existing voluntary consensus standards for metadata common to all open government data"

RPI TWC submitted:
•DCAT - W3C Data Catalog
◦Version controlled on github.
◦Extracted from their CKAN as input to converter.
•VoID - W3C Vocabulary of Interlinked Data
◦Organized datasets by source, dataset, version.
◦Provided links to data dumps, Linksets to LOD.
•PROV - W3C Provenance Interchange Model
◦Captured during CKAN extraction, retrieval, conversion, and publishing.
•Dublin Core Metadata Terms
◦Annotated subjects based on descriptions.

HHS wanted *Classification*

"...classify datasets in our growing catalog, creating entities, attributes and relations that form the foundations for better discovery, integration..."

RPI TWC presented:
•Bottom-up vocabulary and entity reuse
◦Vocabulary created for each dataset
◦Enhanced datasets shifted to reuse vocabulary and entities from other datasets.
◦Three stub vocabularies for top-level reuse.
•NCBO (Nat. Center for Biomedical Ont.) Annotations
◦annotator/annotator.py SADI service
◦data/source/bioontology-org/annotator-description-subject/version/retrieve.sh



Foundations and Trends
Series

Foundations and Trends in Health Web Science

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CV Background slides...

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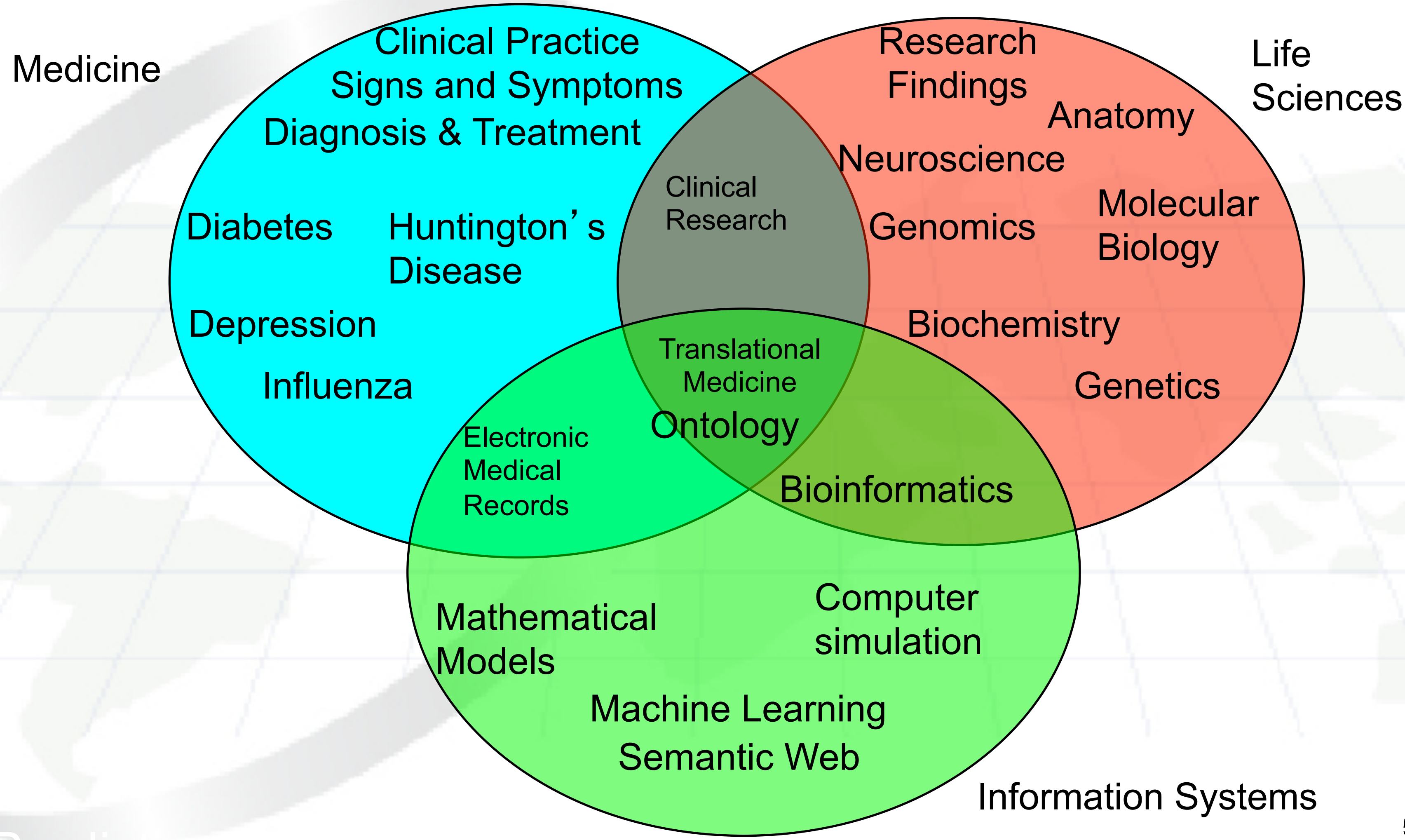
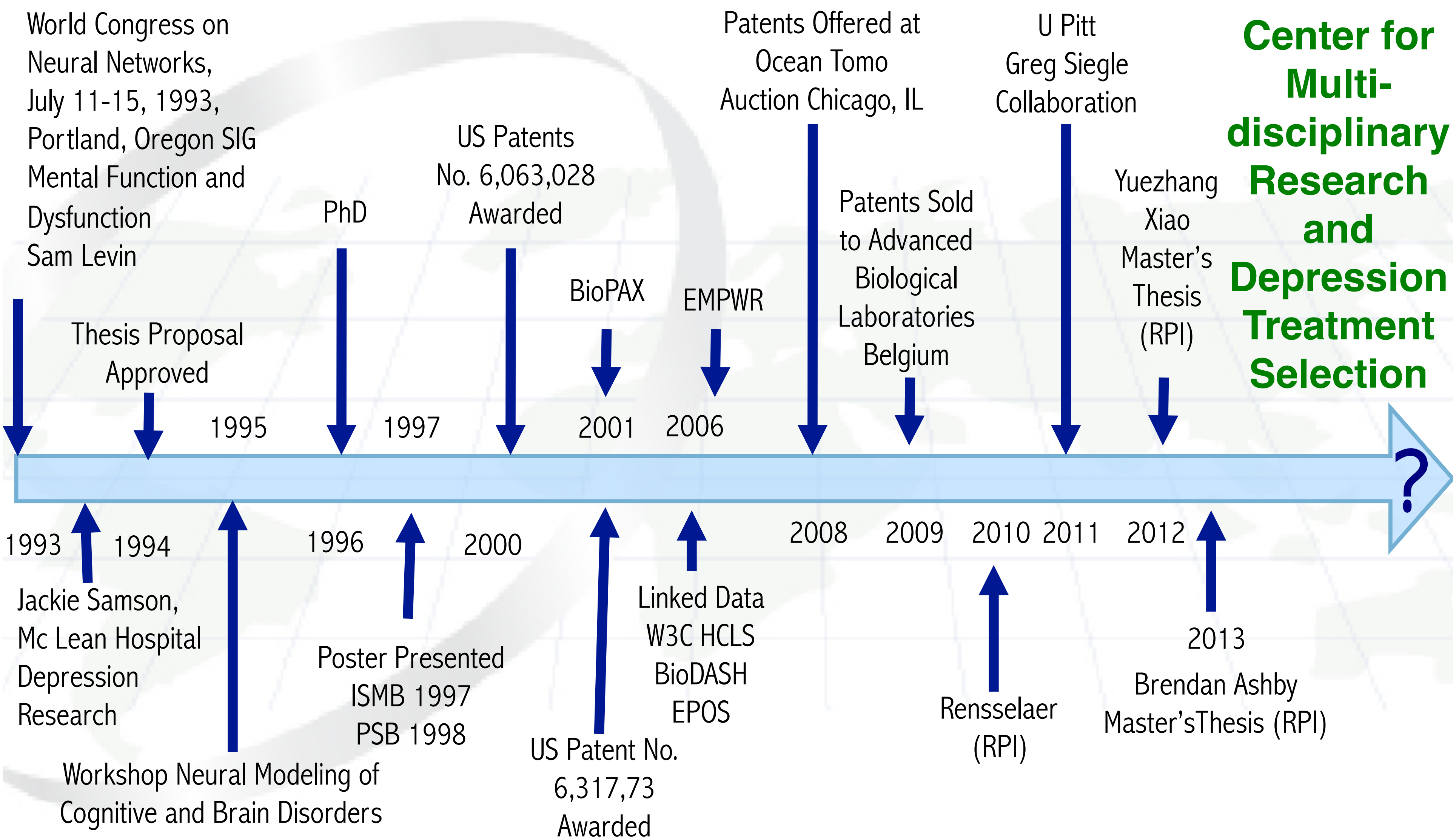
Spanning disciplines
Emerging disciplines



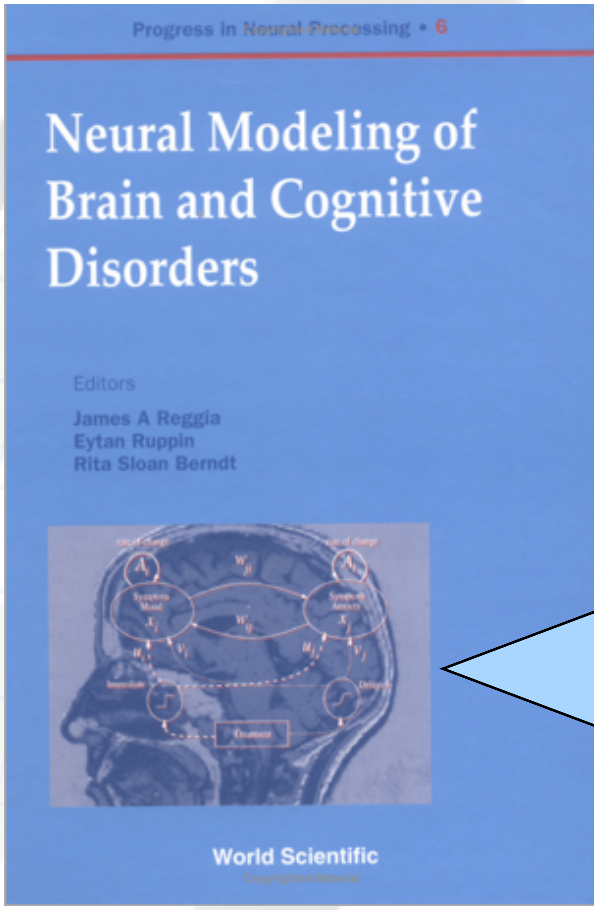
Timeline

(earlier work: 10 years in Software Research & Development and Product Development)



Neural Modeling of Depression

Workshop 1995
Book 1996

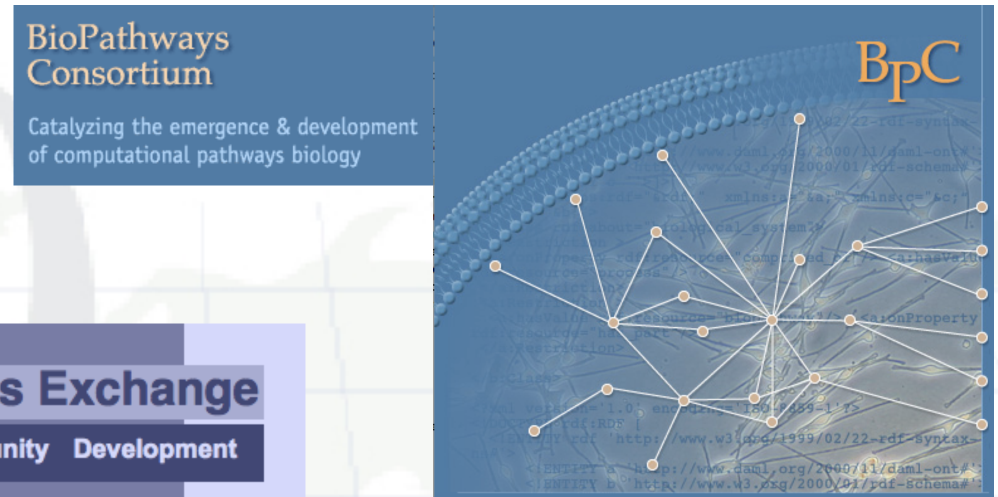


1996 Luciano, J., Cohen, M. Samson, J. ”Neural Network Modeling of Unipolar Depression,” Neural Modeling of Cognitive and Brain Disorders, World Scientific Publishing Company, eds. J. Reggia and E. Ruppin and R. Berndt. Book cover; chapter pp 469-483.

Luciano Model highlighted on book cover

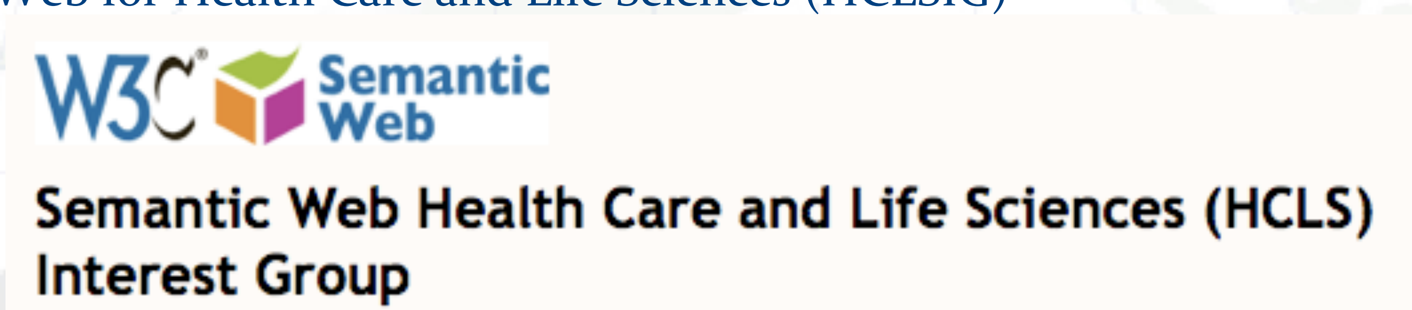
Establishing Communities of Interest/Practice

BioPathways Consortium



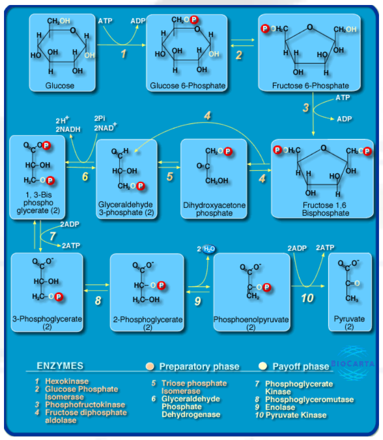
BioPAX

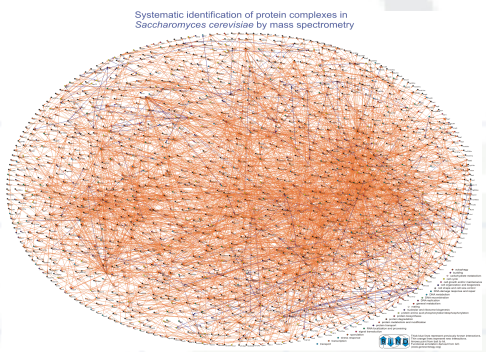
W3C Semantic Web for Health Care and Life Sciences (HCLSIG)

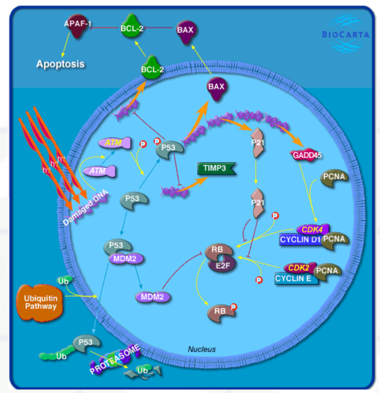


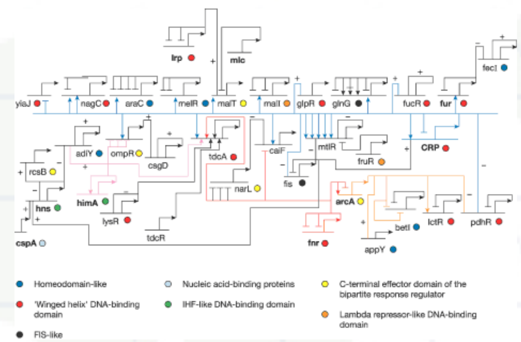
BioPAX - Enabling Cellular Network Process Modeling

Glycolysis | **Protein-Protein** | **Apoptosis** | **TFs in E. coli**









Metabolic Pathways | **Molecular Interaction Networks** | **Signaling Pathways** | **Gene Regulatory Networks**

EMPWR

Collaboration with Manchester, UK

Use instanceStore to reason over BioPAX formatted (OWL) pathway data

- Goal: discover new scientific facts
- Method: Utilize power of reasoners and OWL through coupling BioPAX data and Manchester Technology
- Results: BioPAX semantics lacking thus had to educate BioPAX community and course-correct initiative
- Extending BioPAX to enable the computational exploration

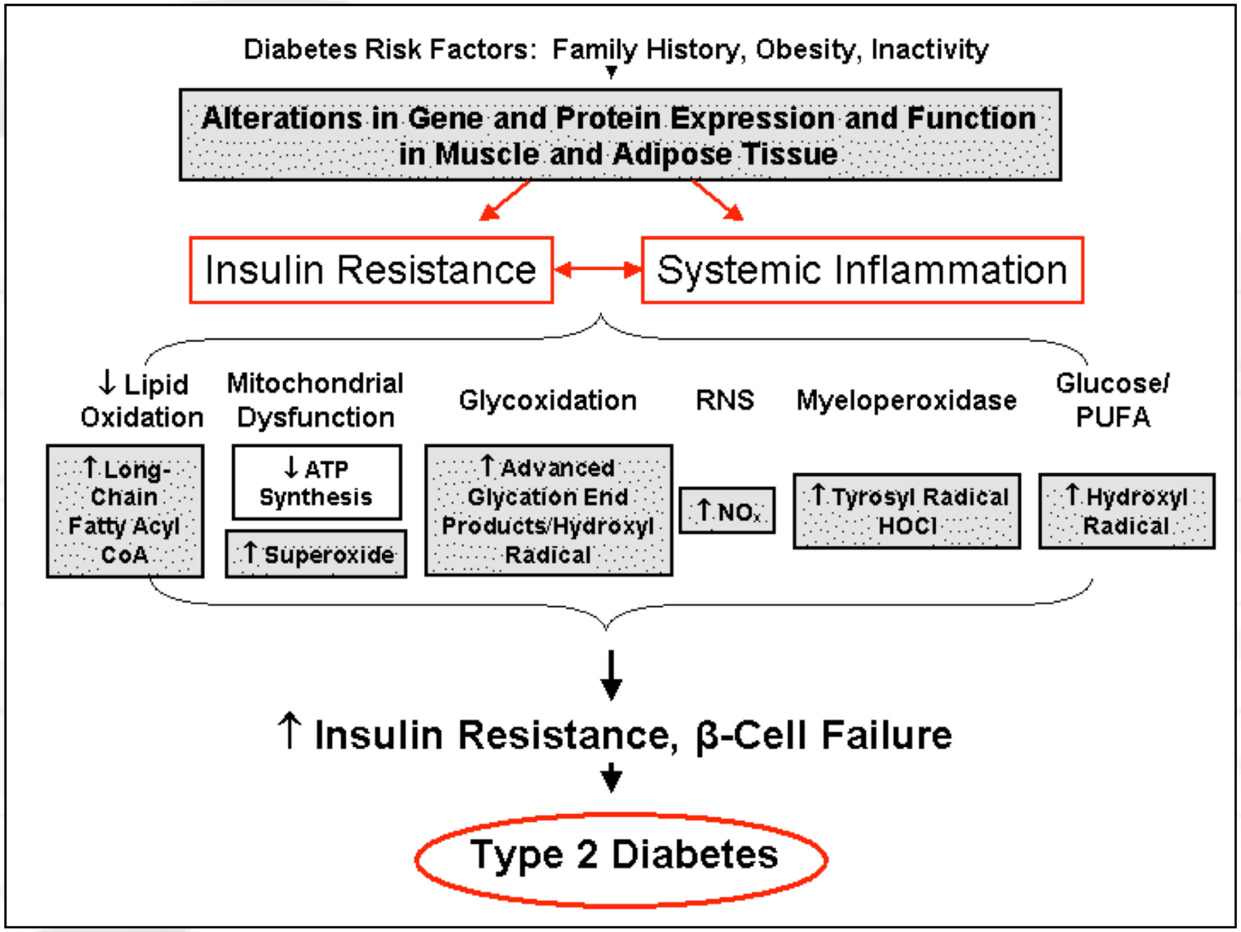
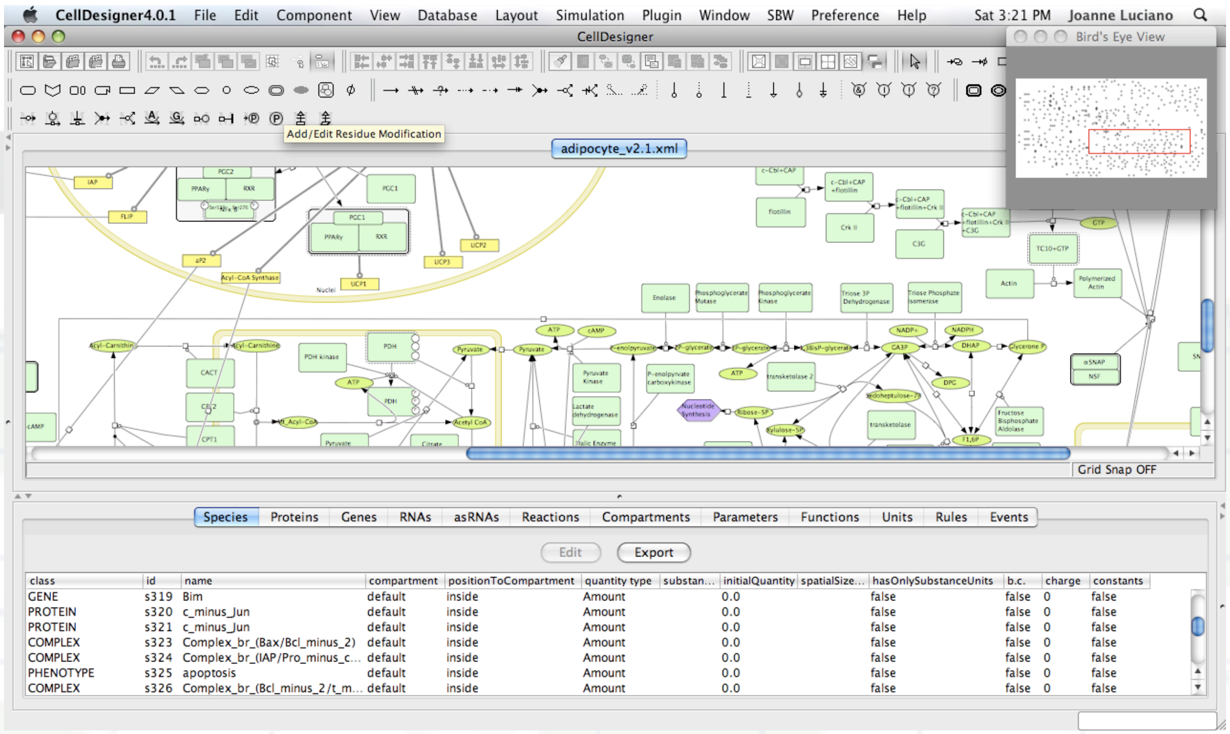


Figure: Integration of genomic and proteomic/metabolomic data (text boxes shaded in gray) proposed for current project. We hypothesize that diabetes risk factors result in altered gene and protein expression in skeletal muscle and adipose tissue (genomic data), leading to insulin resistance and inflammation. This, in turn, results in abnormal tissue function, as indicted by accumulation of long-chain fatty acyl CoA and oxidative damage (proteomic and metabolomic data), further insulin resistance and beta-cell failure, and ultimately to type 2 diabetes

Enhance capability



Cell Designer model of adipose tissue cell. Add gene expression, standard metadata terms (BioPAX, GenBank) Use with expression data constrained by proteomic data towards target ID, biomarker ID, patient population ID

Licensing Opportunities Available

US Patent No. 6,063,028 May 2000

AUTOMATED TREATMENT SELECTION METHOD

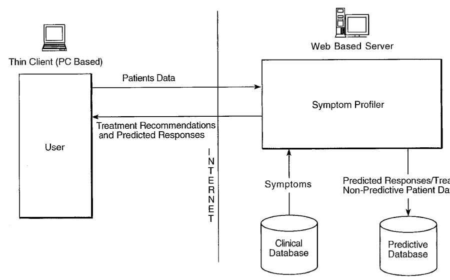
US Patent No. 6,317,731 Nov 2001

METHOD FOR PREDICTING THE OUTCOME OF A TREATMENT

United States Patent [19] Luciano

[11] Patent Number: 6,063,028

[45] Date of Patent: May 16, 2000

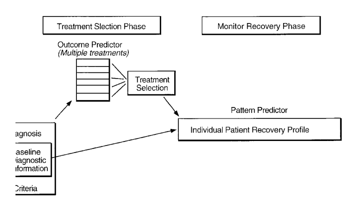


(12) United States Patent Luciano

(10) Patent No.: US 6,317,731 B1

(45) Date of Patent: Nov. 13, 2001

33 Claims, 30 Drawing Sheets



45 Method for predicting the therapeutic outcome of a treatment

Seller:
Joanne S. Luciano

Featured IP Asset:
US 6,317,731

Related IP:
US 6,063,028; US 60/041,287

Expected Value:
$800,000+

Lot Summary:
This Lot features a patent relating to treatment selection. This method is useful for facilitating the choice of a treatment or treatment regime and for predicting the outcome of a treatment for a disorder that is diagnosed and monitored by a clinician. The clinician may be a physician or other appropriately trained and licensed professional. The data used in selecting the optimal choice of treatment and predicting outcomes are derived from the symptoms experienced by a patient.

For one of the assets in the Lot, the system and method disclosed first requires data for a baseline patient profile to be derived reflecting the symptoms experienced by the patient. A set of predictor variables, comprised of predictive symptoms and treatment options, is then defined, relating to data for a baseline patient profile, so that a model representing the relationship between patient response and set of predictor variables can be derived. This model then allows the user to predict the response of the patient to a selected treatment. A model of expected recovery patterns is also derived by integrating individual patterns of known symptoms, responses and treatments. For the other asset an observed symptom and a treatment option are applied to the model disclosed to generate an expected recovery pattern for the patient. Once the treatment is chosen, data from ongoing symptom monitoring can be used with the model to update outcome predictions and assess the requirement for changed or supplementary treatments.

These patent assets are useful to treatment providers, such as hospitals, to disease management companies and health insurers, and to medical software companies. Advantages of the assets are the increased precision achieved by collecting patient data on a continuous basis from clinical studies and updating the model. Unipolar depression is an example of a disorder that can be better understood with the model, however it may find use with other disorders and conditions wherein the patient response to treatment is variable. Also, by applying the observed symptoms of a patient and a proposed treatment option to the predictive model, an expected recovery pattern with greater predictive value is achieved. This method uses symptom monitoring to facilitate earlier intervention and regularly update treatment decisions, and, thus, improving patient care. This model also provides insight into when symptoms improve and in what order. The process allows for a tangible patient symptom response estimate, leading to a potential increase in patient health and well-being.

172 Telemedical Information Management Systems

2009 Sold to Advanced Biomedical Labs (Luxembourg)

Take Home Message

We are shortening the time

and tightening the loop between research and practice, however….

We need to do better - 15 years + is too long, way too long for depressed people to be suffering needlessly.

We must engage all stakeholders and give citizens power over their health data

Research and Practice

- Computational modelers construct *in silico* representations of organic phenomena
- Basic researchers construct *in vitro*
- Clinical Researcher's conduct *in vivo* studies on patient populations
- Clinical practioners apply the results of clinical research