Translational Medicine:
Using Systems of Differential Equations to Identify Patterns in Symptom Remission in Response to Treatment

Knowledge Recovery

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Overview

Why we did this work - to explore the utility of computational methods in medicine

How we did it - used differential equations ("neural networks") to model recovery and compared recovery of two different antidepressant treatments

What we found - recovery patterns for the two treatments were different - the order and timing of improvement of symptoms were different

What we think it means -
  • Improved treatment selection
  • Reduced costs
  • Reduced suffering, possibly saving lives.
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Depression is a BIG 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)

Potential Impact
  1% Improvement would mean 180,000 people helped
  1% Improvement would mean 440 million in savings
The Economic Burden of Depression

Depression is the highest of the health care cost for business

http://www.preventingdepression.com/costs.htm
The Economic Burden of Depression

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

- Rapid transformation of laboratory findings into clinically focused applications
- ‘From bench (computer) to bedside (psychiatrist’s couch) and back’
World Congress on Neural Networks, July 11-15, 1993, Portland, Oregon

SIG Mental Function and Dysfunction Sam Levin

Thesis Proposal Approved

1995

Jackie Samson, McLean Hospital Depression Research

1993

1994

1996

Workshop Neural Modeling of Cognitive and Brain Disorders

1997

Poster Presented ISMB 1997 PSB 1998

1998

2000

US Patents No. 6,063,028 Awarded

2001

US Patent No. 6,317,73 Awarded

2006

Empwr.

2009

Linked Data W3C HCLS BioDASH EPOS

2008

Licensed to Evivar for HIV and Hepatitis B

2007

Patents Offered at Ocean Tomo Auction Chicago, IL

Patents Sold to Advanced Biological Laboratories Belgium

2005

BioPAX

2004

2003

2002

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Research Goals

Illuminate recovery course

Correct Treatment

Individualized Treatment
Today’s talk: Response to treatment

Treatment Response Study

Study #1
analyze path of recovery

Study #2
predict response to treatment

YES
NO
Background

Characteristics

• Clinical Depression (Major Depressive Disorder (MDD))
• Current Treatments

Measurements

• Clinical Symptom (Hamilton Scale)

Problems with current status

• MDD has no sub-diagnosis
• MDD treatment guidelines vague
• MDD treatment not specific to patients
Clinical Data

Symptom Intensity
- Hamilton Depression Rating Scale (0-4 scale)

Treatment
- Desipramine (DMI)
  - Cognitive Behavioral Therapy (CBT)

Outcome
- Recovery studied
  - those patients who responded to treatment
Hamilton Scale for Depression
Example Questions

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)
Modelling

Recast problem into mathematical terms

• Easier to understand
• Easier to manipulate
• Easier to analyze
Understanding Recovery

Depressed → Treatment → Not Depressed

Compare patterns of recovery

- 6 week: When response begins
- 7 symptoms: Indirect (between symptoms)
- 2 treatments: Direct (on symptoms)

(Latency) $\Delta t$
(Interaction Effects) $w$
(Treatment Effects) $u, v$

Recast as dynamical system

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

Depressed → Treatment → Not Depressed

- Symptoms
  - Clinical Data
- Pattern
  - Modeling Recovery
- Outcome
  - Predicting Response
# Data

- **7 Symptoms**
  - (Hamilton questionnaire values measure severity)
  - **Physical:**
    - Early Sleep Disturbance
    - Mid, Late Sleep Disturbance
    - Energy
  - **Performance:**
    - Work & Interests
  - **Psychological:**
    - Mood (sadness, hopelessness)
    - Cognitions (guilt, suicidal)
    - Anxiety

- **2 Treatments**
  - Cognitive Behavioural Therapy (CBT)
  - Desipramine (DMI)

- **Clinical Data**
  - Responders = improvement >= 50%
  - N = 6 patient each study
  - 6 weeks = 252 data points each study
Linking Hypotheses
Symptoms and Brain Region Activity
Overview
Recovery Model and Parameters

Treatment Effects

$u_i, v_i$

Interaction Effects

$w_{ij}$

Latency

$\Delta t$

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Modelling Time to Response

\[
\begin{align*}
    h(\alpha, t-\Delta t) &= \frac{1}{1 + e^{-\alpha(t-\Delta t)}} \\
    \alpha & \quad \text{Rapidness of response} \\
    \Delta t & \quad \text{Latency}
\end{align*}
\]
Modelling Treatment Effects

2 Models
- CBT
- DMI

Optimized parameters specify model
Initial conditions predict patient trajectory
Recovery Model Equation

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

- **Acceleration of symptom**
- **Stabilizing factor**
- **Rate of symptom change**
- **Interactions between symptoms**
- **Immediate effect step function**
- **Treatment Effects on each symptom (strength)**
- **Delayed effect sigmoid function**
- **Steepness**
- **Latency**
Training the model

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

- Obtain optimized parameters
  - fit patient data
  - train on time course
  - minimize error term \( L \)
  - gradient descent on parameters

\( L = \) Error term
\( X = \) data
\( i = \) symptoms
\( P_j = \) parameter
\( k = \) patients
Results of Training (treatment group)

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

(b) Predicted and actual mean patterns of recovery (DMI)

CBT

DMI
Results of Training
(Example CBT Patient)
(we’re not there yet)
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Results

Optimized parameters specify model
Initial conditions predict pattern trajectory
Latency

$\Delta t = \text{response delay}$

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

Cognitive Behavioral Therapy

- Anxiety
- Cognitions
- Mood
- Work
- Energy
- E Sleep
- M, L Sleep

Desipramine

- Immediate vs. 1.2 Weeks
- Immediate vs. 3.4 Weeks

coefficients (strength)

Immediate ($u_i$) vs. Delayed ($v_i$)
Treatment Direct Effects
Immediate and Delayed
Treatment Effects and Interaction Effects

CBT Sequential

DMI (delayed) CONCURRENT
Order and Time of Symptoms Improve is Different for CBT and DMI
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Conclusions

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

• Suggests CBT better serves patients with strong cognition and mood symptoms DMI may better serve patients with all the symptoms but are not suicidal

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