Multiscale mathematical approaches for translational mental health benefits

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Presentation plan

Background and conceptual basis
  - hierarchies of cognition

Mechanism of cognition I
  - mood and bipolar disorder

Mechanism of cognition II
  - (trauma) memory and PTSD
Background
Team and support
Conceptual Basis
Hierarchies of cognition

_Cognition_; the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.

**mood; a state of mind**

**neuron firing pattern**

**brain oscillations**

**coupled neuron oscillations**
Hierarchies of cognition

Learning how to scale across disparate temporal (and spatial) processes is one of our objective.
Mechanisms of cognition I
Mood and bipolar disorder

1-4% of all adults suffer from this mental illness.

Classically characterized by mood swings between depression and mania.

Yet these are episodes are relatively infrequent and the focus is on inter-episode mood variation as a target for treatment.
Mood and bipolar disorder

Illustration: Inter-episodic mood instability marked by **

Manic episode

Depressed episode

Time →
Mood and bipolar disorder

![Graph of QIDS Score over time (Weeks)]
Mood(y) times with statistics
Threshold Autogressive Time Series Modelling

Fit statistical models of the form:

\[ y(t) = X(t)\theta^{(j)} + \sigma^{(j)}\epsilon(t) \text{ if } r_{(j-1)} < \bar{y} < r_{(j)} \]

with following likelihood structure:

\[
L(P \mid Y) = \frac{Y_{1,j}^{r-1} \left( \frac{r}{\mu_1} \right)^r \exp \left(-\left(\frac{r}{\mu_1}\right) Y_{1,j}\right)}{\Gamma(r)} \prod_{k=2}^{T} \frac{Y_{k,j}^{r-1} \left( \frac{r}{\mu_k} \right)^r \exp \left(-\left(\frac{r}{\mu_k}\right) Y_{k,j}\right)}{\Gamma(r)}
\]

Markov Chains: QIDS analysis

For an individual patient we can work out the transitions from one QIDS state to another on a state space.

Define the state space in terms of three QIDS rankings:

\[
\begin{pmatrix}
    p(0 \rightarrow 0) & p(0 \rightarrow < 9) & p(0 \rightarrow \geq 9) \\
    p(< 9 \rightarrow 0) & p(< 9 \rightarrow < 9) & p(< 9 \rightarrow \geq 9) \\
    p(\geq 9 \rightarrow 0) & p(\geq 9 \rightarrow < 9) & p(\geq 9 \rightarrow \geq 9)
\end{pmatrix}
\]
(Holmes et al. 2016 Translational Psychiatry e720)
Overview

Aggregate-level

Time series analysis of mood fluctuations can be achieved using appropriate ML formulations and missing value algorithms.

Patient-level

Simple stochastic models provide a useful tool to analysis mood and treatment interventions

(Holmes et al. 2016 Translational Psychiatry e720)
Relaxing with oscillations
Relaxation oscillators and mood variation

Mood fluctuations through time are unknown function of (let’s say) two processes, $X$ and $Y$:

$$M(t) = \alpha t + \beta X + \gamma Z$$

$$\frac{dM}{dt} = \frac{\partial M}{\partial t} + \frac{\partial M}{\partial X} \frac{\partial X}{\partial t} + \frac{\partial M}{\partial Z} \frac{\partial Z}{\partial t}$$

$$\frac{dM}{dt} = \alpha + \beta \frac{\partial X}{\partial t} + \gamma \frac{\partial Z}{\partial t}$$
Relaxation oscillators and mood variation

Define each of processes as a relaxation oscillator:

\[
\frac{dx}{dt} = y(t) - f(x) \quad \frac{dy}{dt} = \frac{-x(t) - a}{b}
\]

\[
f(x) = -x(t) + \frac{x^3}{3}
\]

System has fixed values \( x^* = -a \), \( y^* = -a + a^3 / 3 \) and is stable if as \( b \to 0 \) and \( a \neq [-1,1] \).
Relaxation oscillators and mood variation

(Bonsall et al. 2015 JRSI doi: 10.1098/rsif.2015.0670)
Threshold Autogressive Time Series Modelling

Fit statistical models of the form:

\[ y(t) = X(t)\theta^{(j)} + \sigma^{(j)}\epsilon(t) \text{ if } r_{(j-1)} < \bar{y} < r_{(j)} \]

with following likelihood structure:

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\]

Threshold Autoregressive Time Series Modelling

AR(1) and TAR(1) models with QIDS score against weeks.

AR(2) and TAR(2) models with QIDS score against weeks.

Best fit AR model: AR1 57%, AR2 29%, TAR1 7%, TAR2 7%.
Autogressive Time Series Modelling

Fit statistical models under following likelihood structure:

$$L(P \mid Y) = \frac{Y_{1,j}^{r-1} \left( \frac{r}{\mu_1} \right)^r \exp \left( - \left( \frac{r}{\mu_1} \right) Y_{1,j} \right)}{\Gamma(r)} \prod_{k=2}^{T} \frac{Y_{k,j}^{r-1} \left( \frac{r}{\mu_k} \right)^r \exp \left( - \left( \frac{r}{\mu_k} \right) Y_{k,j} \right)}{\Gamma(r)}$$

$$\mu_k = \int_{k-T}^{k} [\alpha + \beta X(v) + \gamma Z(v)] dv$$
Linking mood model to mood observations

The diagram shows a scatter plot with two axes: RO(1) parameter value on the x-axis and RO(2) parameter value on the y-axis. The plot is divided into four regions:

- RO(2) stable and both ROs stable
- RO(2) stable and both ROs unstable
- Both ROs stable
- RO(1) stable

Each region is marked with different colors and symbols to indicate the stability of the RO parameters.
Linking mood model to mood observations

\[ L(P \mid Y) = \frac{Y_{1,j}^{r-1} \left( \frac{r}{\mu_1} \right)^r \exp \left( - \left( \frac{r}{\mu_1} \right) Y_{1,j} \right)}{\Gamma(r)} \prod_{k=2}^{T} \frac{Y_{k,j}^{r-1} \left( \frac{r}{\mu_k} \right)^r \exp \left( - \left( \frac{r}{\mu_k} \right) Y_{k,j} \right)}{\Gamma(r)} \]
Overview

Aggregate-level

Oscillator frameworks provide a robust way to scale between mood and lower levels of neuron organisation.

Patient-level

Stochastic versions provide robust tools to describe mood variation and highlight patient-specific idiosyncrasies.

(Bonsall et al. 2015 JRSI doi: 10.1098/rsif.2015.0670)
Scaling neuronal heights
Scaling across mechanisms of cognition

Mood fluctuations through time are unknown function of (let’s say) two processes, \(X\) and \(Y\):

\[
M(t) = \alpha t + \beta X + \gamma Z
\]

\[
\frac{dM}{dt} = \frac{\partial M}{\partial t} + \frac{\partial M}{\partial X} \frac{\partial X}{\partial t} + \frac{\partial M}{\partial Z} \frac{\partial Z}{\partial t}
\]

\[
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\[f(x) = -x(t) + \frac{x^3}{3}\]

System has fixed values \(x^* = -a, y^* = -a + a^3 / 3\) and is stable if as \(b \to 0\) and \(a \neq [-1,1]\)
Scaling across mechanisms of cognition

Collective neuron dynamics can be described by aggregated processes through coupled ODE processes (e.g. Wilson & Cowan 1972):

\[
\frac{dn_e}{dt} = -n_e(t) + S(F_e)(k_e - r_en_e(t))
\]

\[
\frac{dn_i}{dt} = -n_i(t) + S(F_i)(k_i - r_in_i(t))
\]

\(S(F_j)\) represents firing threshold functions of the form, for example:

\[
S(F_j) = \frac{1}{1 + \exp(-v_j(F_j))}
\]

With weighted coupling (Fj):

\[
F_j = w_{jj}n_k - w_{jl}n_l
\]
Scaling across mechanisms of cognition

*How do we scale neuron process to mood level?*

Assume that mood processes operate on a temporal scale $t$ and that there are $n$ iterations of the neuron dynamics each last $\Delta T$

We can define $\Delta Tn = t$ and the neuron-dynamics can be represented (to second order) as a finite-difference expression:

$$\mu(t - \Delta T) = \mu(t) - f(\mu(t - \Delta T))\Delta T - \frac{1}{2} f(\mu(t - \Delta T))(\Delta T)^2$$

*So no need to average over the fast dynamics*
Scaling across mechanisms of cognition

\[\mu(t - \Delta T) = \mu(t) - f(\mu(t - \Delta T))\Delta T - \frac{1}{2} f(\mu(t - \Delta T))(\Delta T)^2\]

\[\mu(t) = \mu(t - \frac{t}{n}) + f\left(\mu\left(t - \frac{t}{n}\right)\right)\frac{t}{n} - \frac{1}{2} f\left(\mu\left(t - \frac{t}{n}\right)\right)\left(\frac{t}{n}\right)^2\]

Numerically, neuron dynamics (within mood dynamics) can implemented through a 2\textsuperscript{nd} order RK methods to solve the small-time delay approximation:

\[\mu(t) = \mu\left(t - \frac{t}{n}\right) + (a_1 k_1 + a_2 k_2)\frac{t}{n}\]
Scaling across mechanisms of cognition

\[ \frac{dM}{dt} = \alpha + \beta(\mu) \frac{\partial X}{\partial t} + \gamma(\mu) \frac{\partial Z}{\partial t} \]
Mechanism of cognition II
Trauma memory, interventions and graphs

Cognition; the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.
Trauma memory, interventions and graphs

(iyadurai et al. 2018 Molecular Psychiatry, 23, 674–682)
Trauma memory, interventions and graphs

(Porcheret et al. 2020 Sleep in press)
Markov Chains: trauma is a graph

- Trauma State
- Labile (reactivated) Memory
- Consolidated iMemory
- Neutral Task Memory

Transitions:
- \[ p_1 \]
- \[ 1 - p_1 \]
- \[ p_2 \]
- \[ 1 - p_2 \]
- \[ p_3 \]
- \[ 1 - p_3 \]

Probabilities:
- \[ p = 1.0 \]
Markov Chains: dynamics

(A) Probability of staying in labile memory states (p3) vs. Strength of reminder cue ($\alpha$)

(B) Probability of staying in labile memory states (p3) vs. Strength of reminder cue ($\alpha$)
Bounds on trauma: Cauchy-Schwarz Inequality

Eigenvalues for transition matrices are often labelled:

\[ 1 = \lambda_1 > \lambda_2 \geq \cdots \geq \lambda_T \]

For Markov chains,

\[ \lambda_* = \max |\lambda|, \lambda \neq 1 \]

Spectral gap (difference of moduli of first two dominant eigenvalues) and hence relaxation time to convergence (\( \tau \)) are,

\[ \gamma = 1 - \lambda_* \quad \tau = \frac{1}{\gamma} \]

*Use this to work out how long memories stay ‘mixed’.*
Bounds on trauma: Cauchy-Schwarz Inequality

But, how fast is convergence?; what is the upper bound on the convergence of the Markov chain ($P'$) to a fixed state ($\pi$)

Or, how long do memories stay mixed before absorbing into a state?

$$||P' - \pi|| \geq 0$$

This needs a definition of a distance metric – we chose total variation distance measure, such as:

$$||P' - \pi|| = \frac{1}{2} [\phi P' - \pi]$$
Bounds on trauma: Cauchy-Schwarz Inequality

So,

\[
\left( \frac{1}{2} [\varphi P' - \pi] \right)^2 \geq 0
\]

Working this through yields a Cauchy-Schwarz inequality:

\[
P'^2 \pi^2 \geq (P' \pi)^2
\]

Square of the products must be less than the product of the squares (for memories to stay mixed)
Bounds on trauma: Cauchy-Schwarz Inequality

Upper bound on speed at which memories ‘relax’ into neutral state

Pr of staying in the labile memory state (p3)
Bounds on trauma: Cauchy-Schwarz Inequality

From translational benefit, maintaining memories in a probability state may be good enough....
Summary

Computational and mathematical approaches to clinical psychology allow us to do *mood maths*:

- **Moody times with statistics**
  - formulating appropriate time series allows aggregate and patient-level predictions

- **Relaxing with oscillators**
  - allow a scaling between different levels of dynamics

- **Scaling neuronal heights**
  - don’t average over fast dynamics (lost all information) but scale dynamics

- **Trauma memory, interventions and graphs**
  - can be investigated as discrete stochastic processes
Questions?