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

mathematical ecology

Background

mathematical
ecology

Team and support








Karolinska Institutet

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wellcome

THE ROYAL SOCIETY

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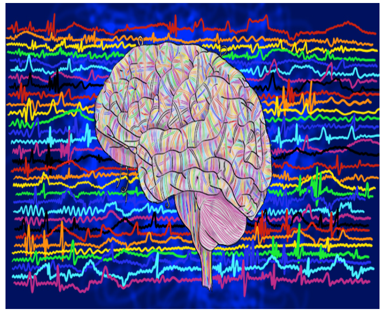
Conceptual Basis

Hierarchies of cognition

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

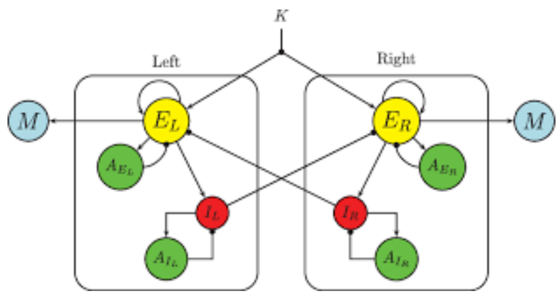
mood; a state of mind



brain oscillations

neuron firing pattern

coupled neuron oscillations



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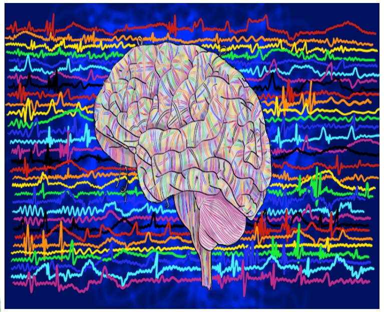
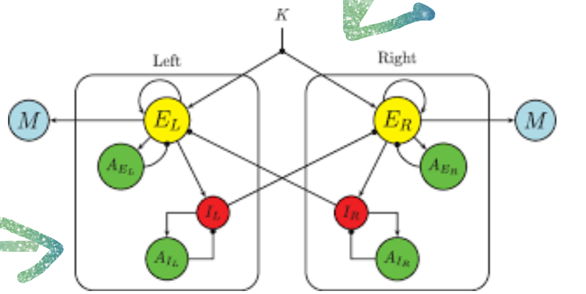
Hierarchies of cognition

Learning how to scale across disparate temporal (and spatial) processes is one of our objective





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Mechanisms of cognition I

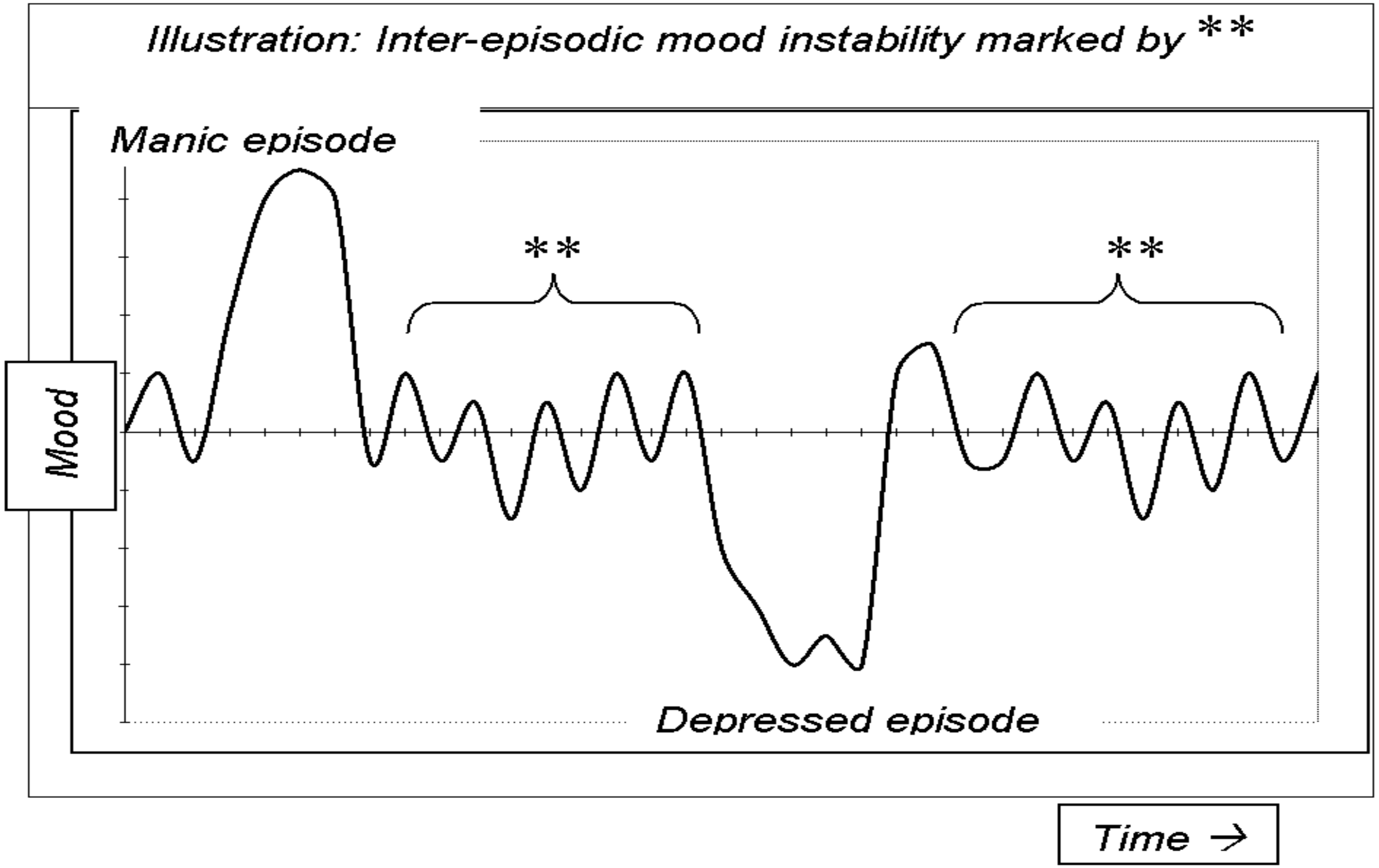
Mood and bipolar disorder

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

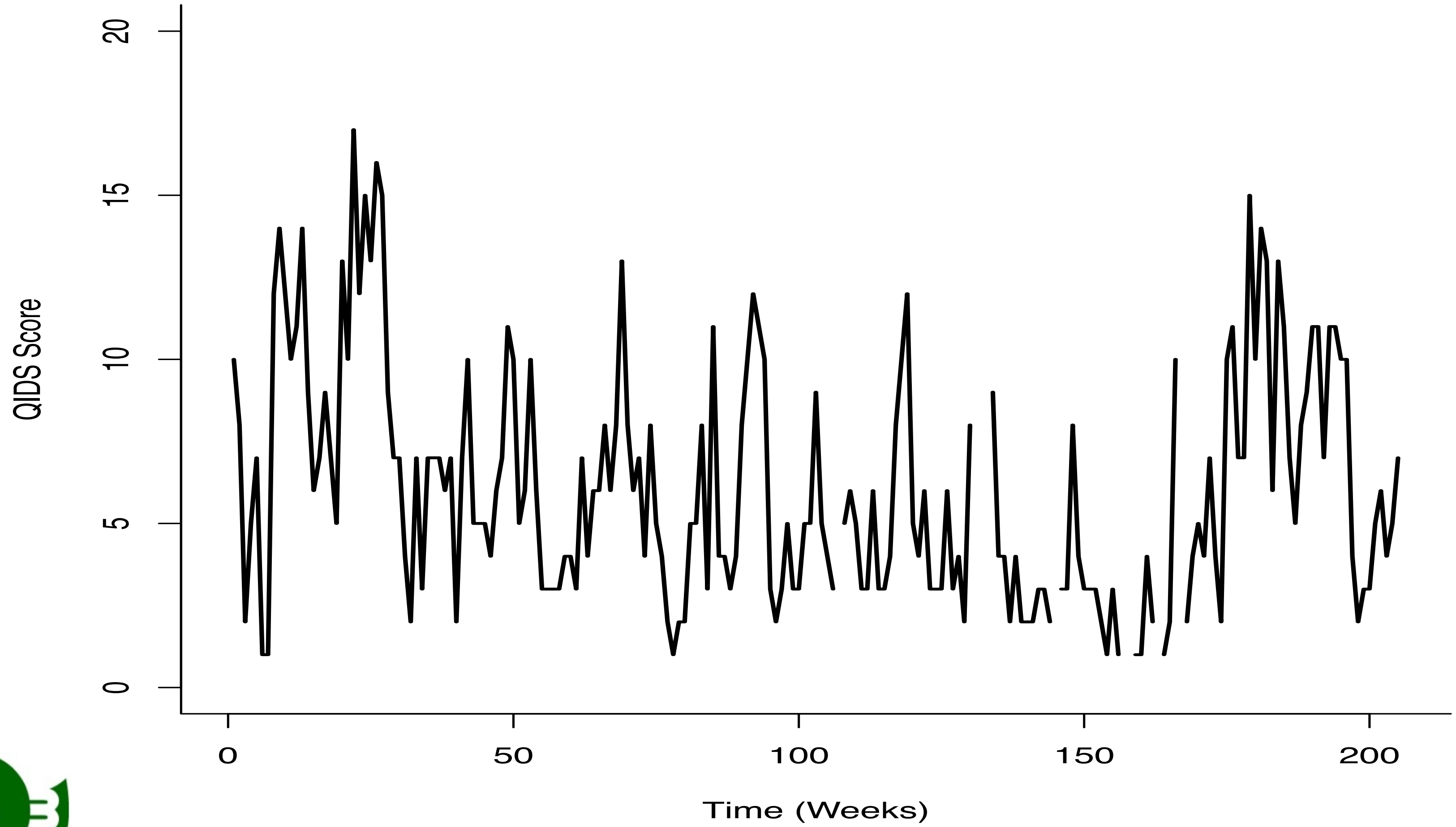
Classically characterized by mood swings between depression and mania

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



Mood and bipolar disorder



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Mood(y) times with statistics

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Threshold Autogressive Time Series Modelling

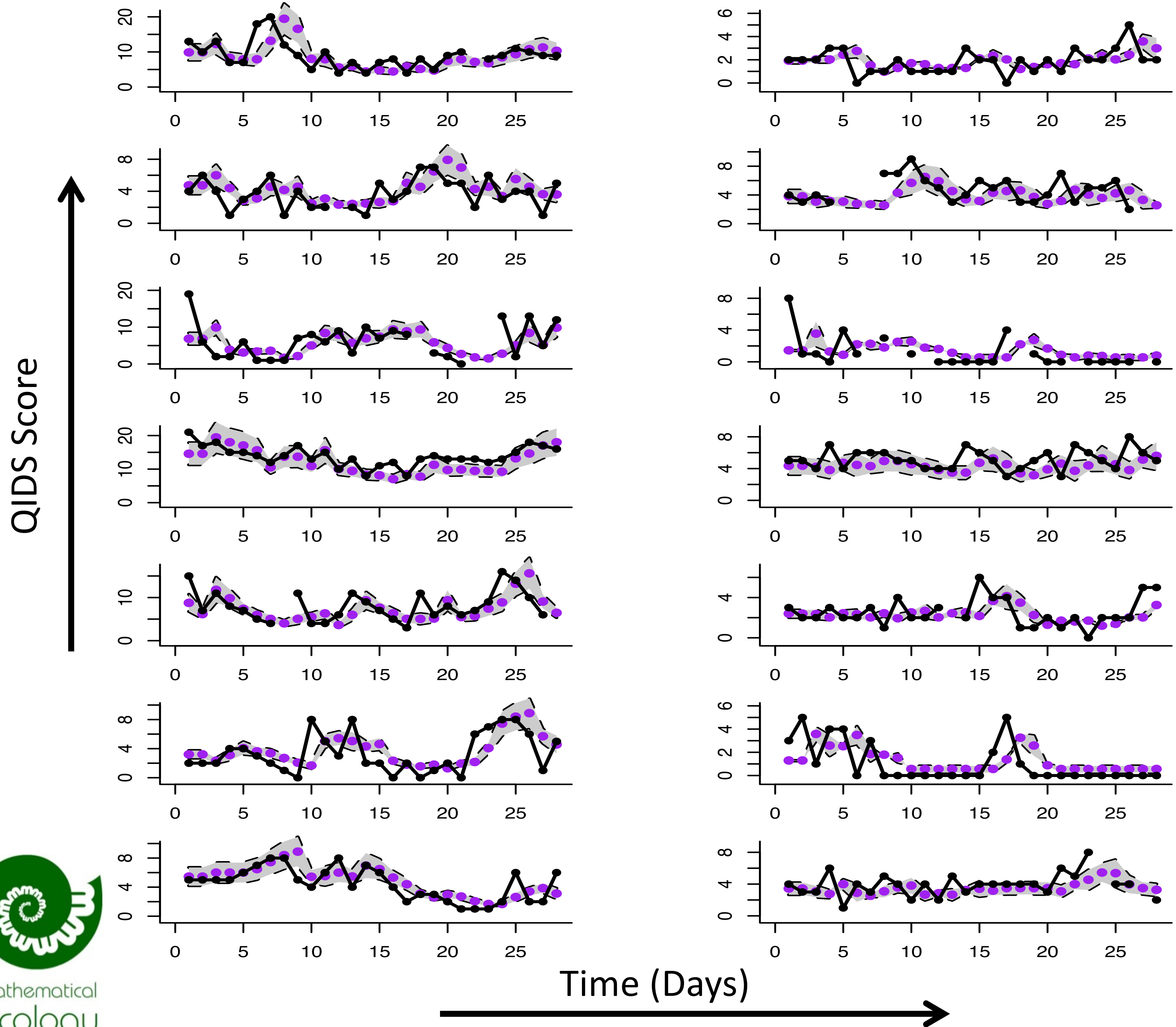
Fit statistical models of the form:

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

with following likelihood structure:

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

(Bonsall et al. 2012 Proc R. Soc Lond B. 279(1742):3632)



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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:

$$\begin{pmatrix} p(0 \to 0) & p(0 \to < 9) & p(0 \to \geq 9) \\ p(<9 \to 0) & p(<9 \to <9) & p(<9 \to \geq 9) \\ p(\geq 9 \to 0) & p(\geq 9 \to <9) & p(\geq 9 \to \geq 9) \end{pmatrix}$$

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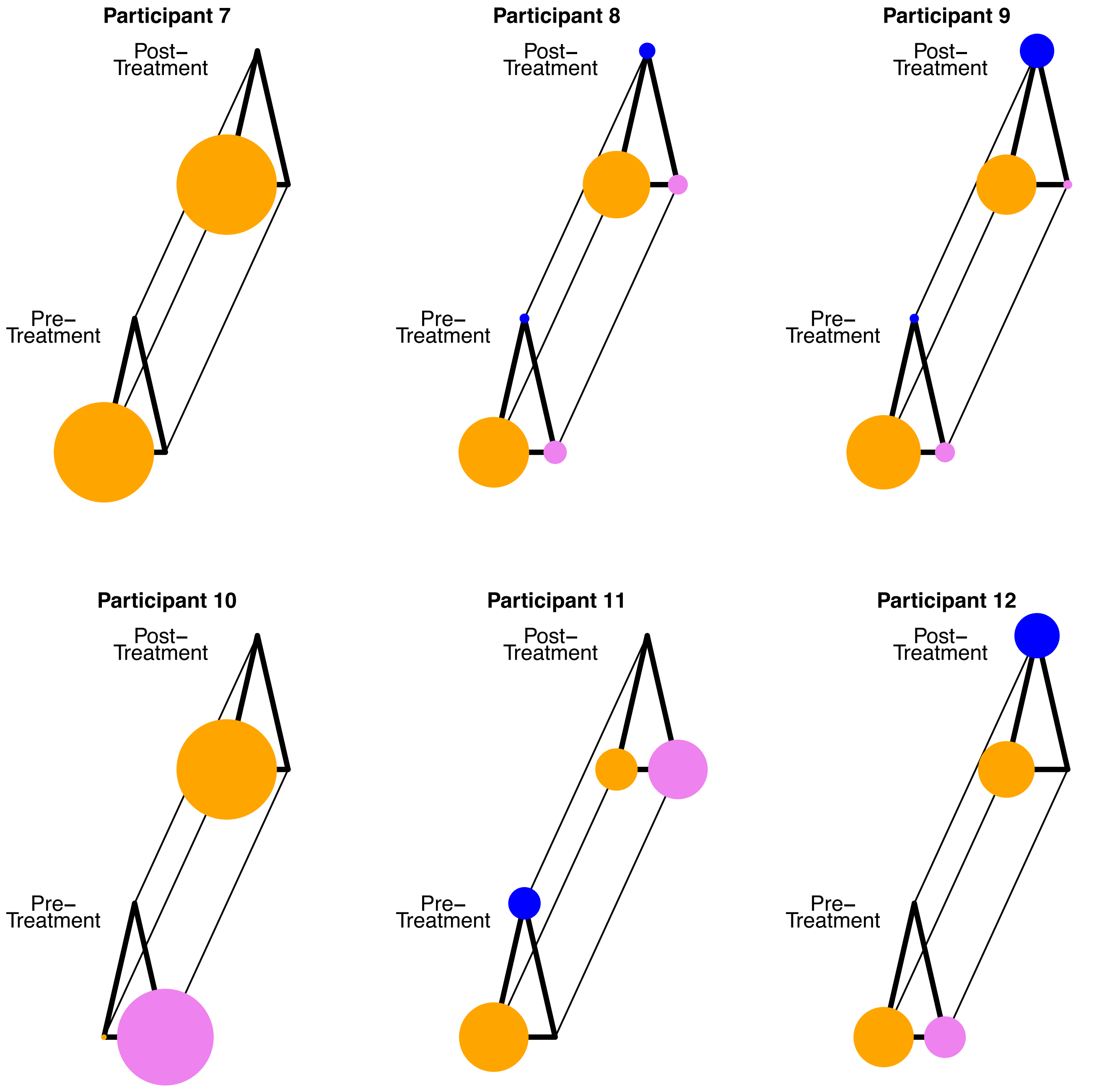

(Holmes et al. 2016 Translational Psychiatry e720)

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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

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(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*:

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

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

$$\frac{dM}{dt} = \alpha + \beta\frac{\partial X}{\partial t} + \gamma\frac{\partial Z}{\partial t}$$

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Relaxation oscillators and mood variation

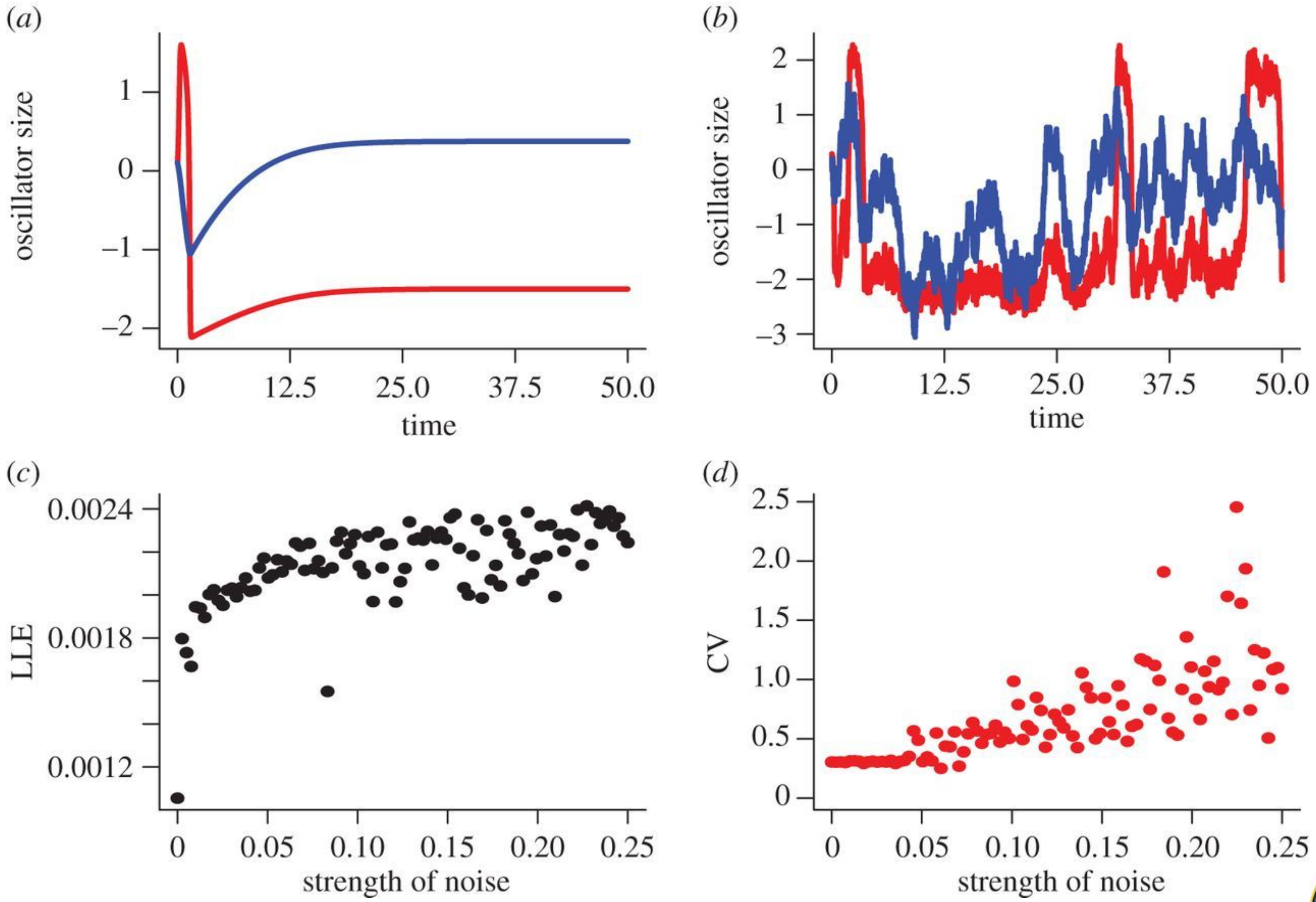
Define each of processes as a relaxation oscillator:

$$\frac{dx}{dt} = y(t) - f(x) \qquad \frac{dy}{dt} = \frac{-x(t) - a}{b}$$

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

System has fixed values $x^* = -a$, $y^* = -a + a^3/3$ and is stable if as b→0 and $a \neq [-1,1]$

Relaxation oscillators and mood variation



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(Bonsall et al. 2015 JRSI doi: 10.1098/rsif.2015.0670)

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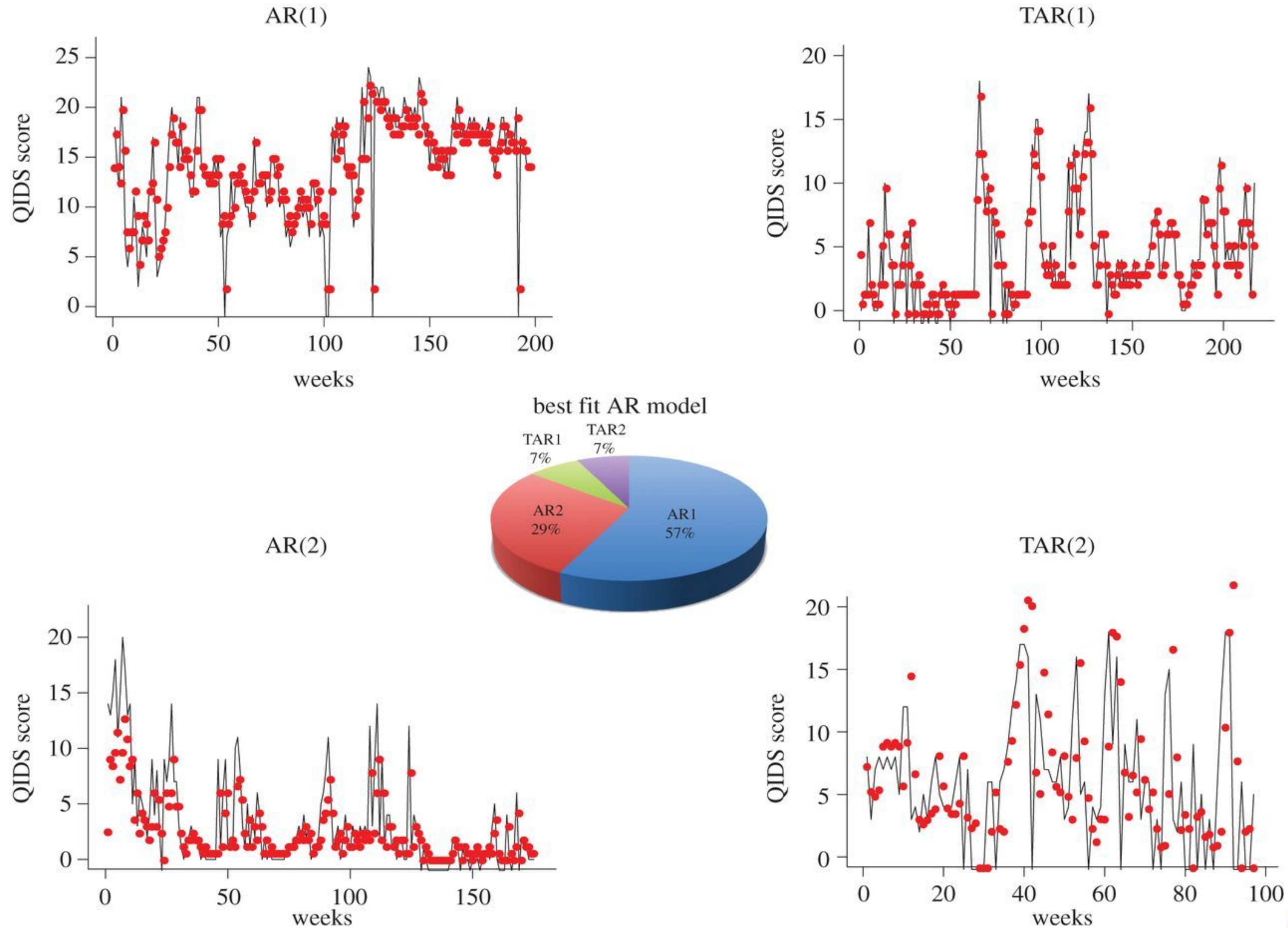
(Bonsall et al. 2012 Proc R. Soc Lond B. 279(1742):3632)

Threshold Autoregressive Time Series Modelling



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Autogressive Time Series Modelling

Fit statistical models under following likelihood structure:

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

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

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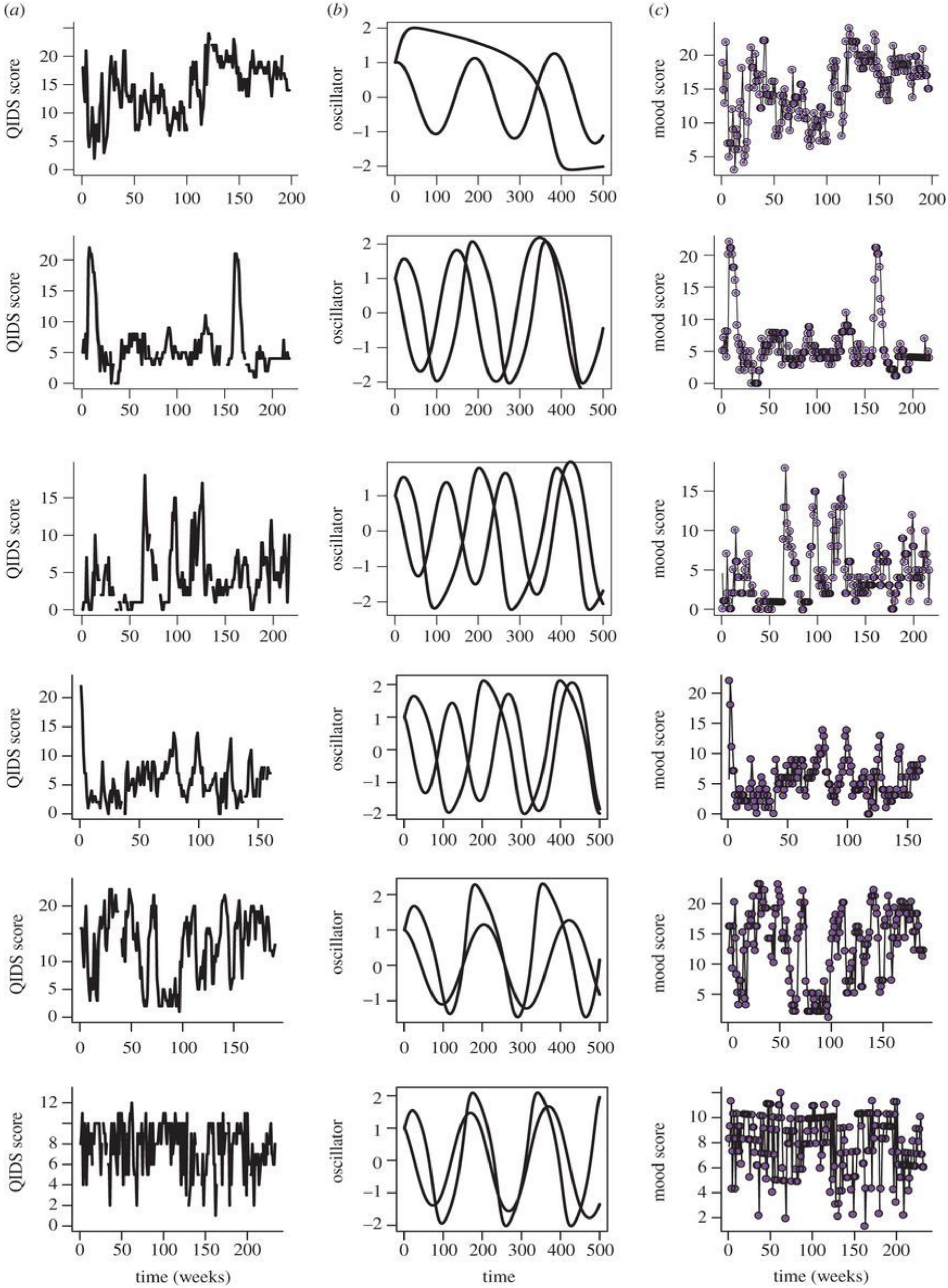
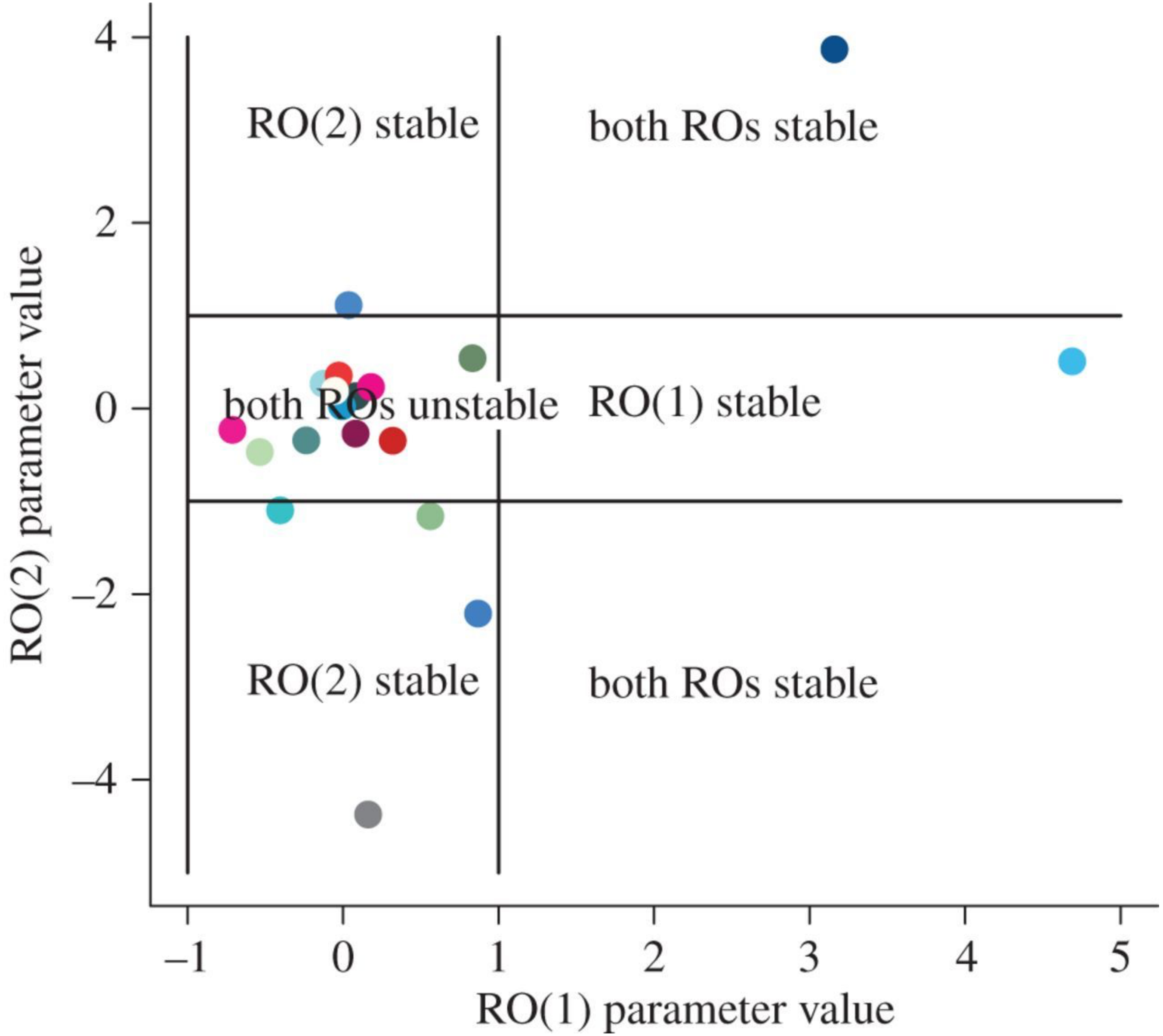


(a)
(b)
(c)
QIDS score
oscillator
mood score
time (weeks)
time
time (weeks)

Linking mood model to mood observations



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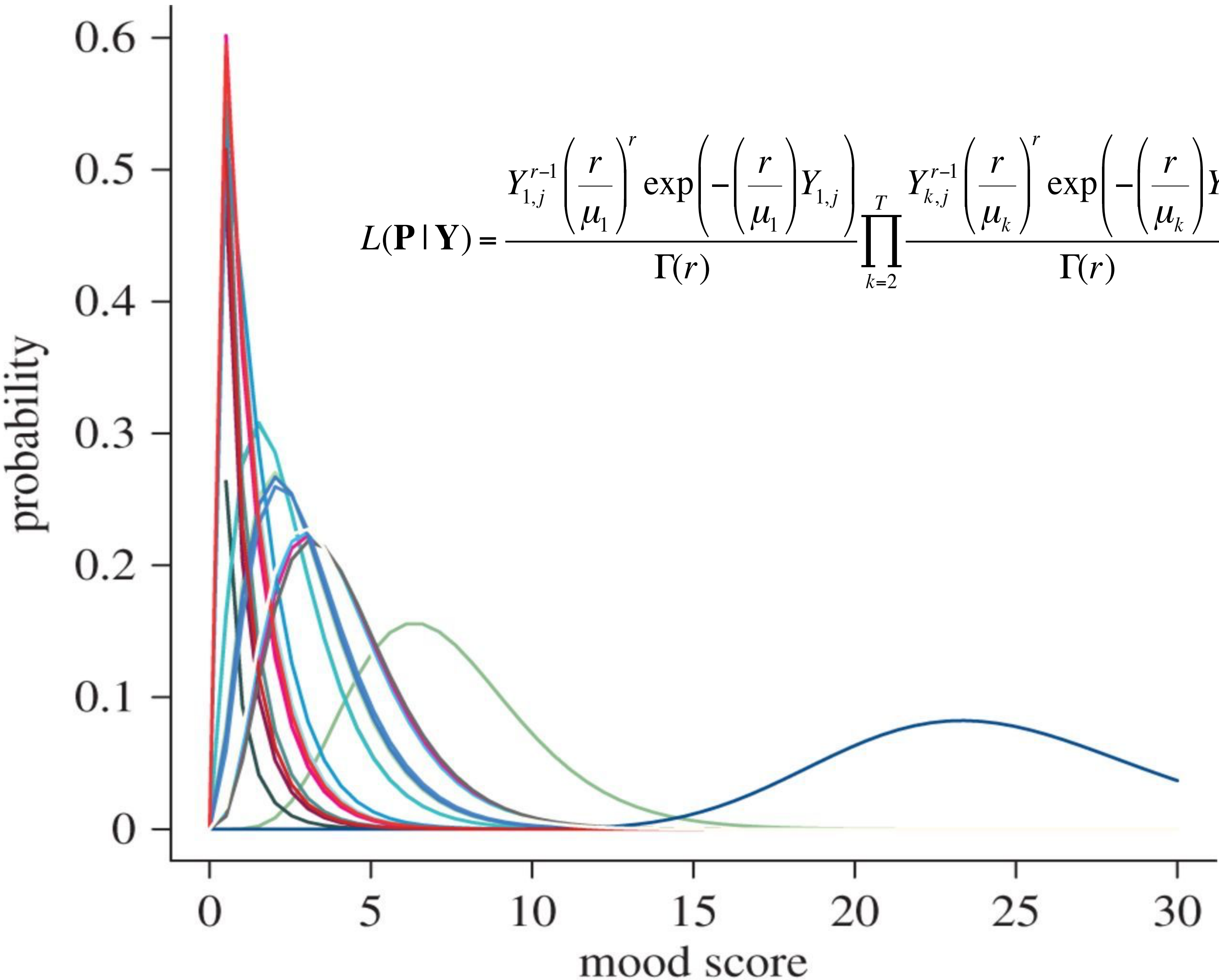
Linking mood model to mood observations



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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.

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(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*:

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

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

$$\boxed{\frac{dM}{dt} = \alpha + \beta\frac{\partial X}{\partial t} + \gamma\frac{\partial Z}{\partial t}}$$

Relaxation oscillators and mood variation

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System has fixed values $x^* = -a$, $y^* = -a + a^3/3$ and is stable if as b→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):

$$\frac{dn_e}{dt} = -n_e(t) + S(F_e)\big(k_e - r_e n_e(t)\big)$$

$$\frac{dn_i}{dt} = -n_i(t) + S(F_i)\big(k_i - r_i n_i(t)\big)$$

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

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

With weighted coupling (Fj) :

$$F_j = w_{jj} n_k - w_{jl} n_l$$

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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 ΔT

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

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

So no need to average over the fast dynamics

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Scaling across mechanisms of cognition

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

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

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

$$\mu(t) = \mu\left(t-\frac{t}{n}\right) + (a_1 k_1 + a_2 k_2)\frac{t}{n}$$

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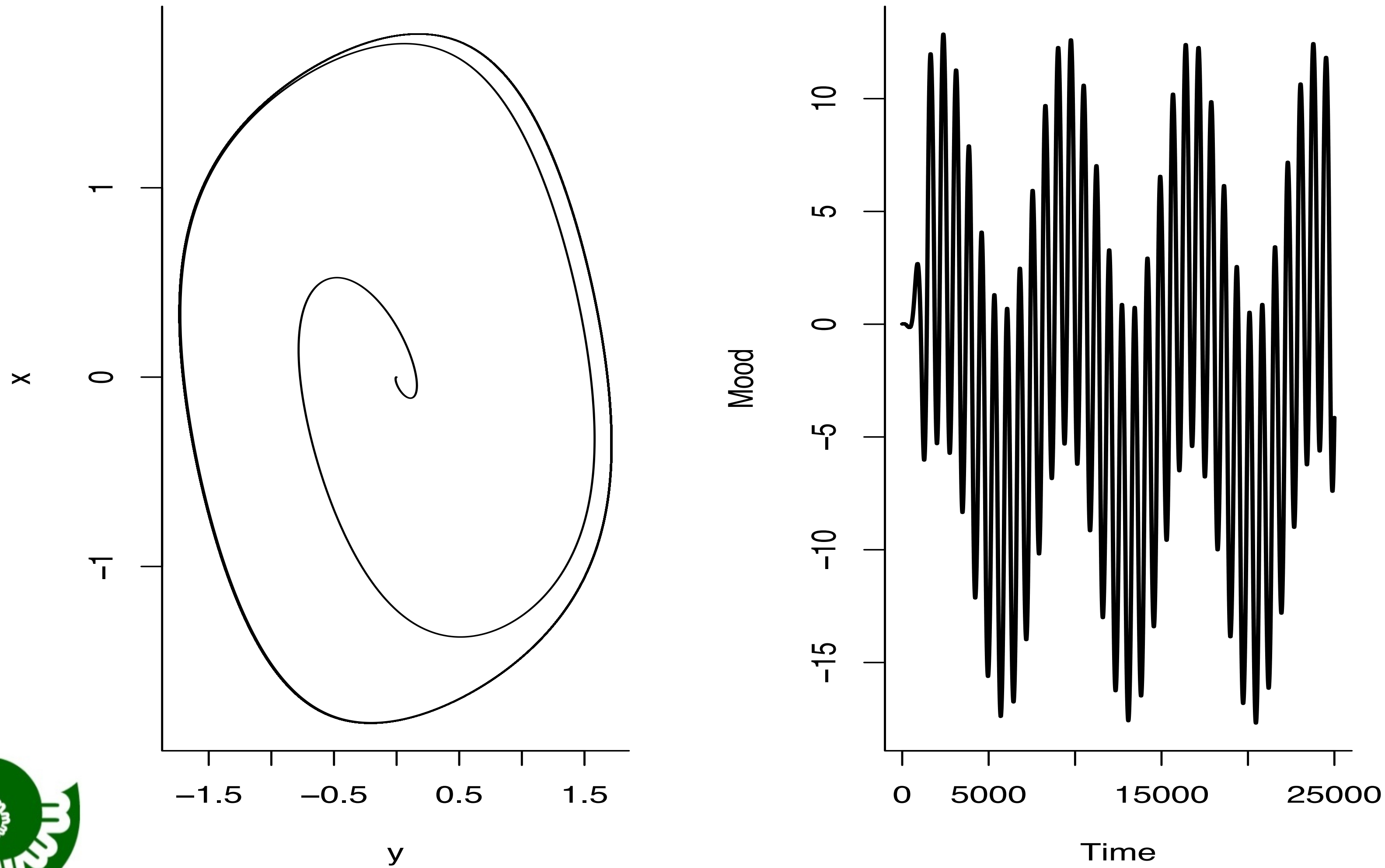
Scaling across mechanisms of cognition

$$\frac{dM}{dt} = \alpha + \beta(\mu)\frac{\partial X}{\partial t} + \gamma(\mu)\frac{\partial Z}{\partial t}$$



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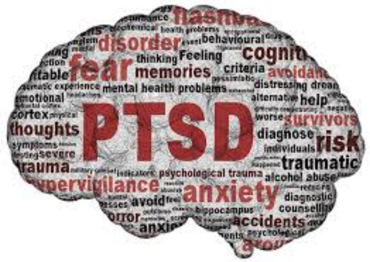
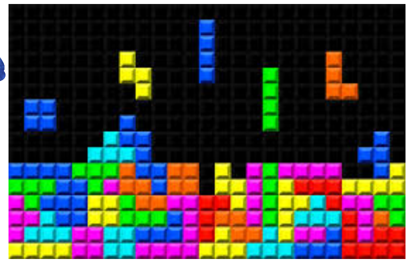
Mechanism of cognition II

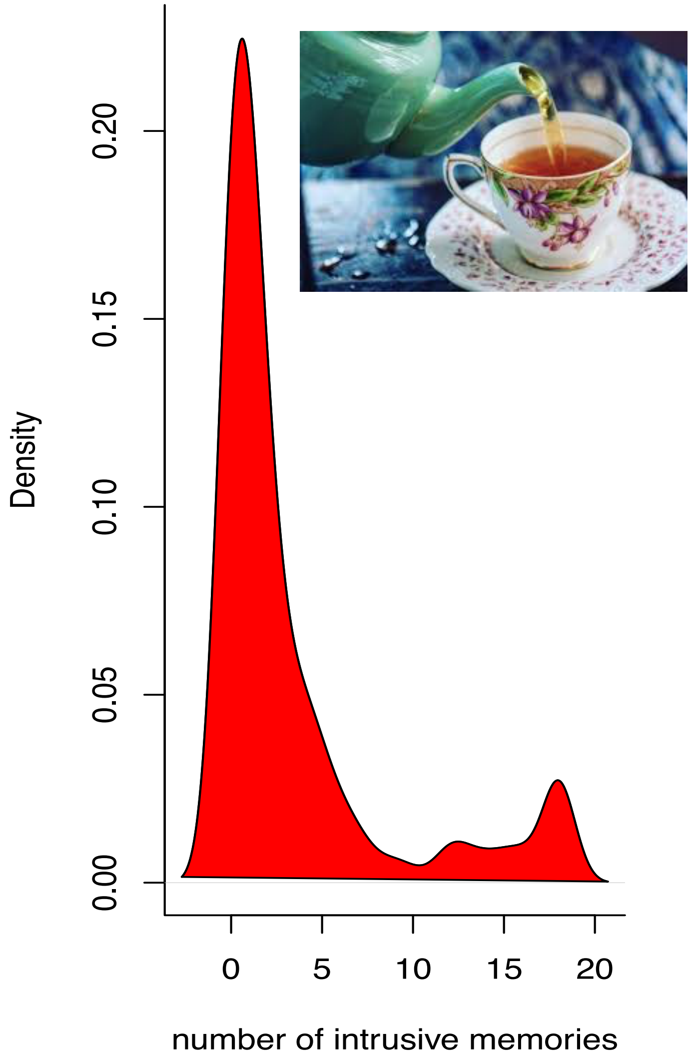
Trauma memory, interventions and graphs

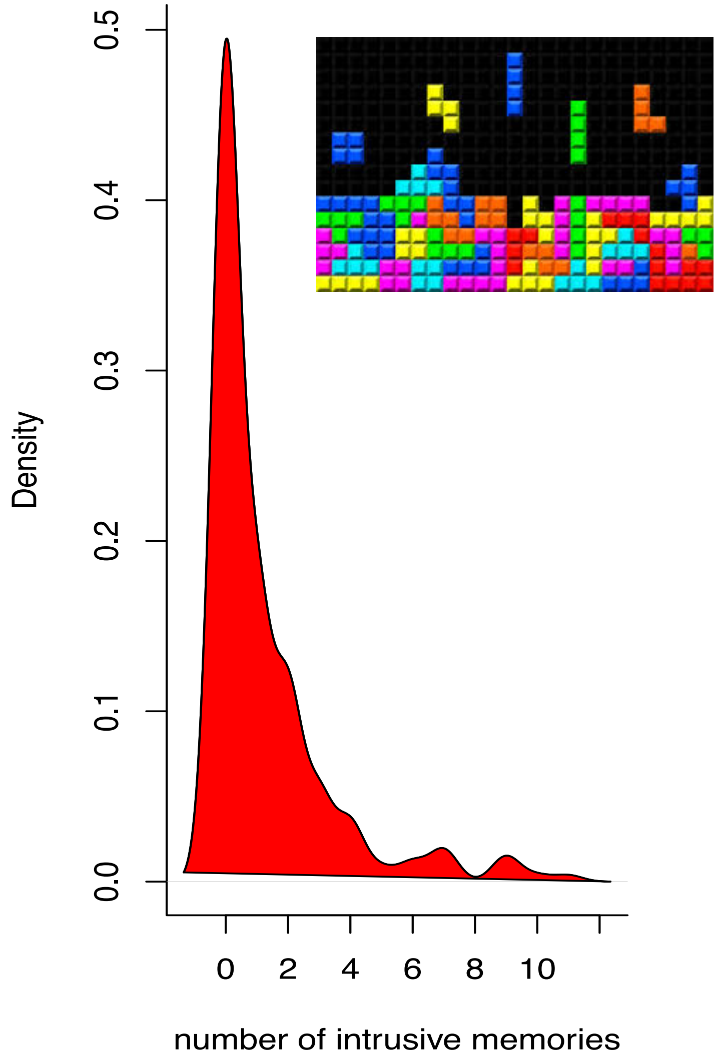
Cognition; the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses





Trauma memory, interventions and graphs





(Iyadurai et al. 2018 Molecular Psychiatry, 23, 674–682)

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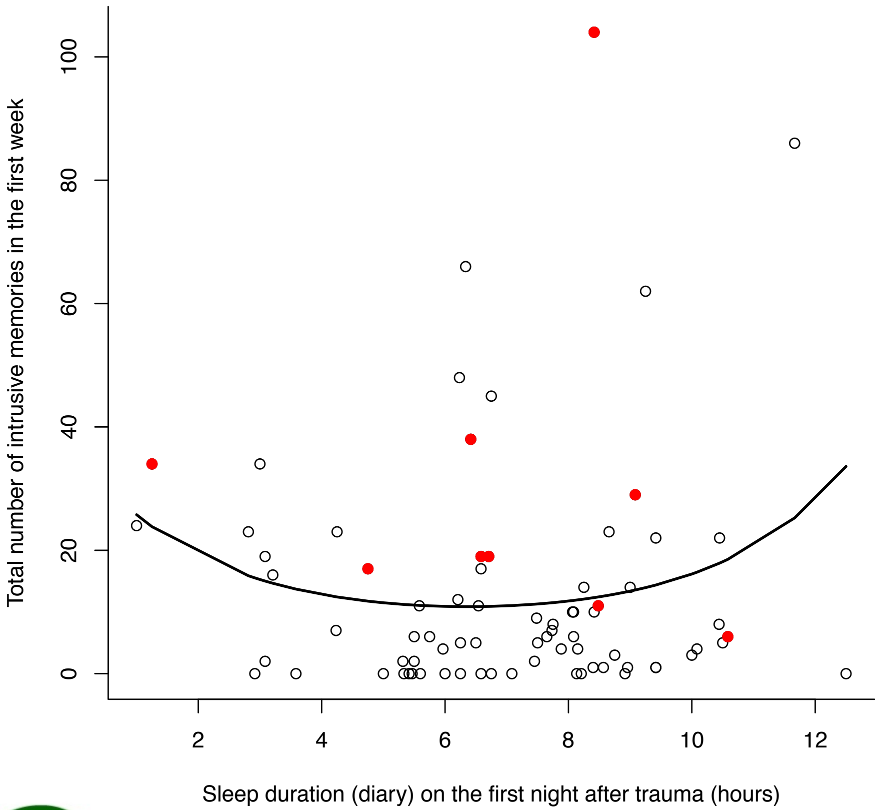
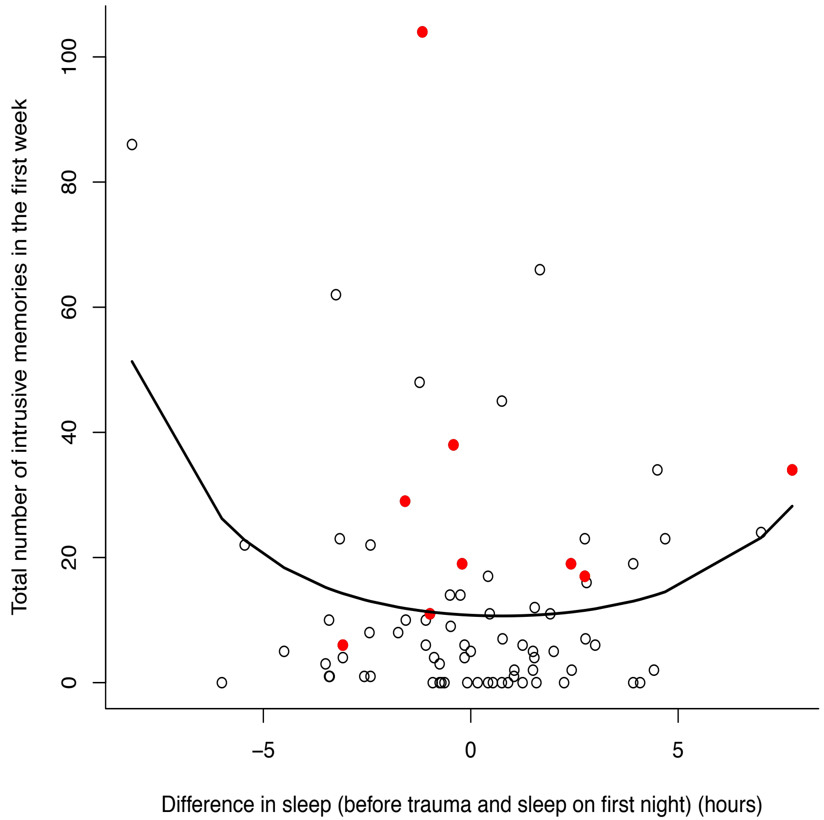
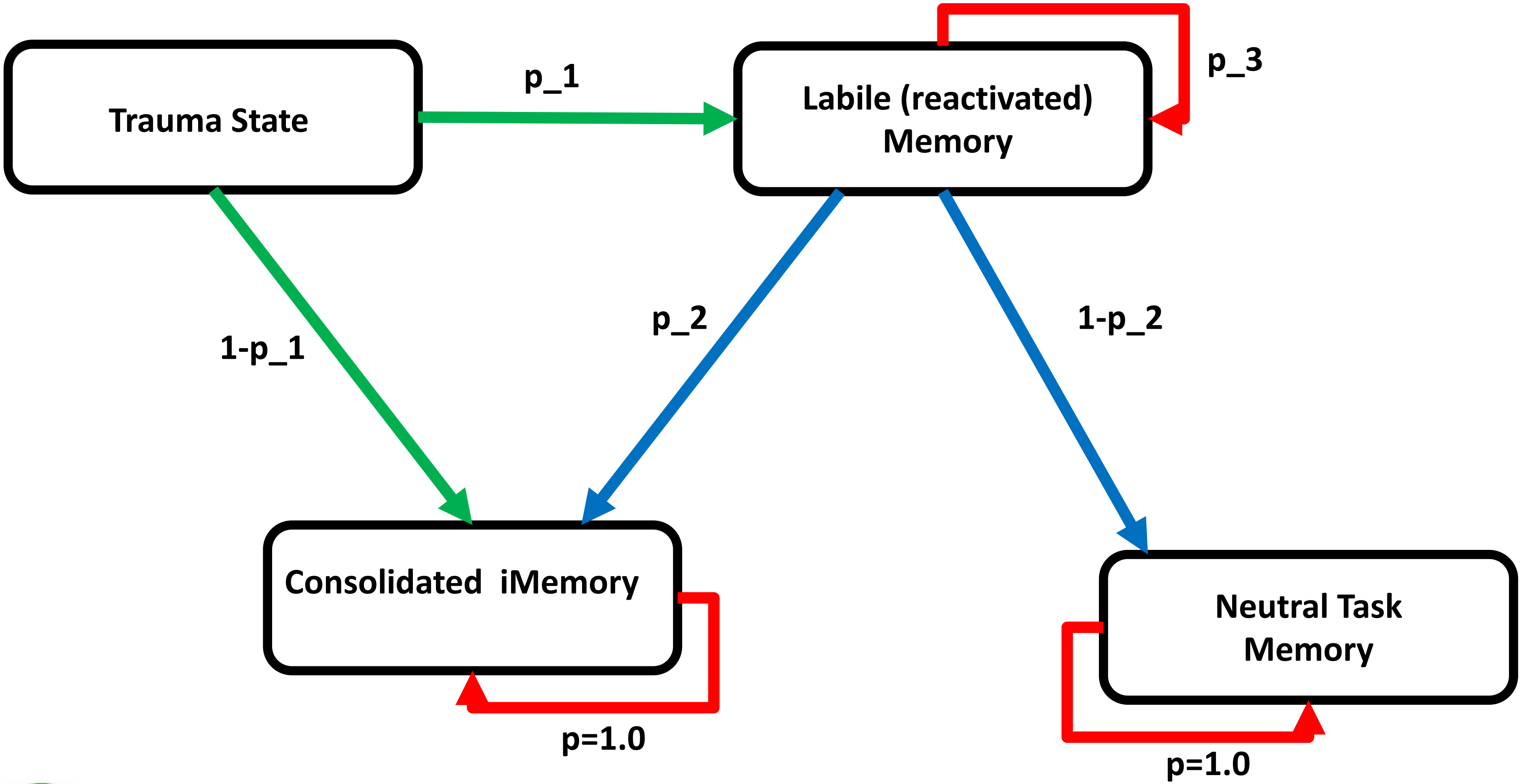
Trauma memory, interventions and graphs





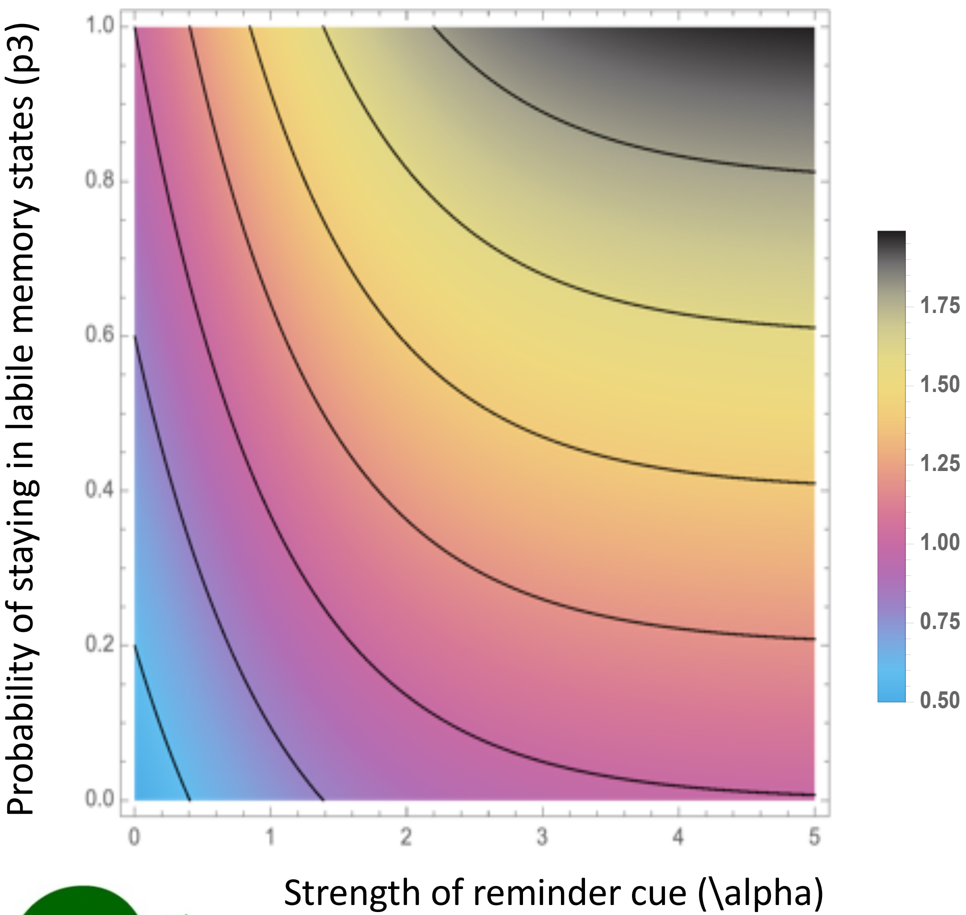
(Porcheret et al. 2020 Sleep *in press*)

Markov Chains: trauma is a graph

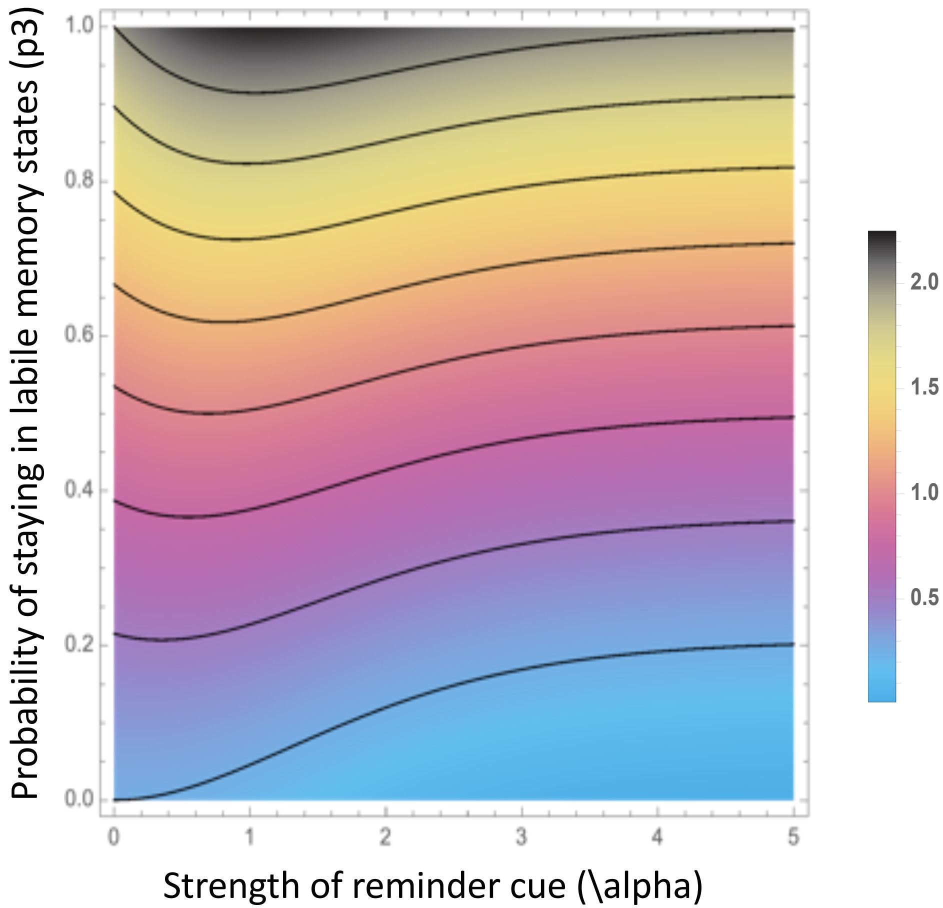


Markov Chains: dynamics

(A)



(B)



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 (τ) are,

$$\gamma = 1 - \lambda_* \qquad \tau = \frac{1}{\gamma}$$

Use this to work out how long memories stay 'mixed'.

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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 (π)

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

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

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

$$\left|\left|P' - \pi\right|\right| = \frac{1}{2}\left[\varphi P' - \pi\right]$$

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Bounds on trauma: Cauchy-Schwarz Inequality

So,

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

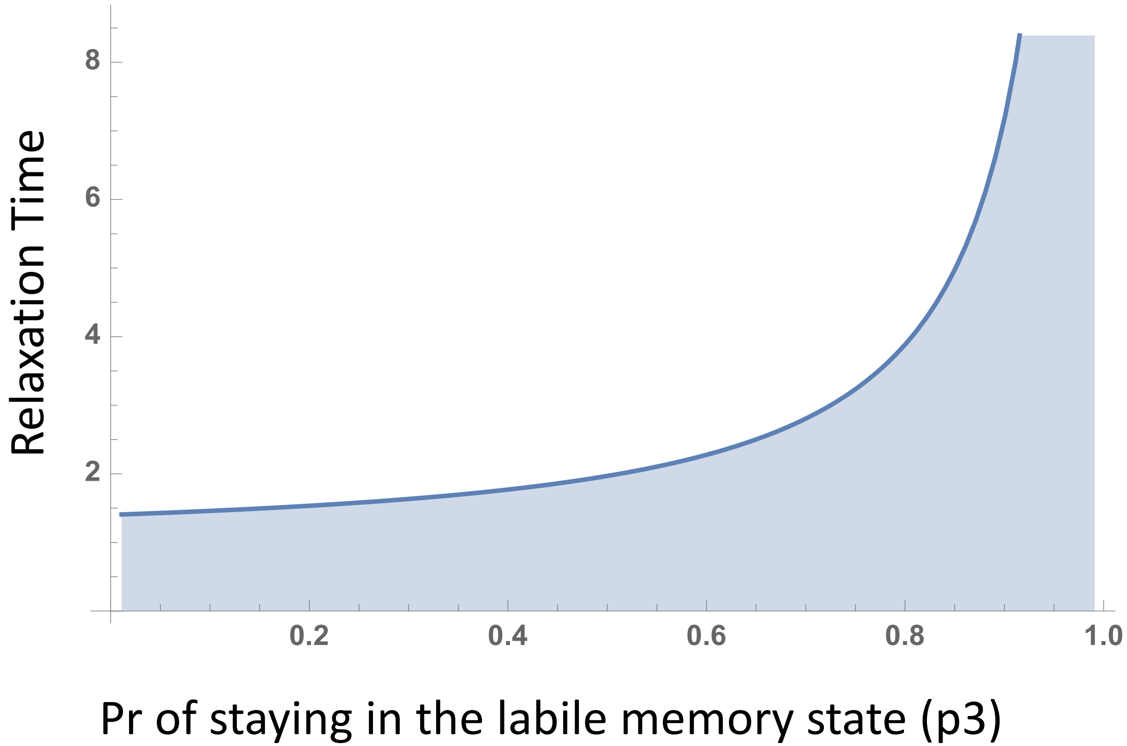
Working this through yields a Cauchy-Schwarz inequality:

$$P'^2\pi^2 \geq (P'\pi)^2$$

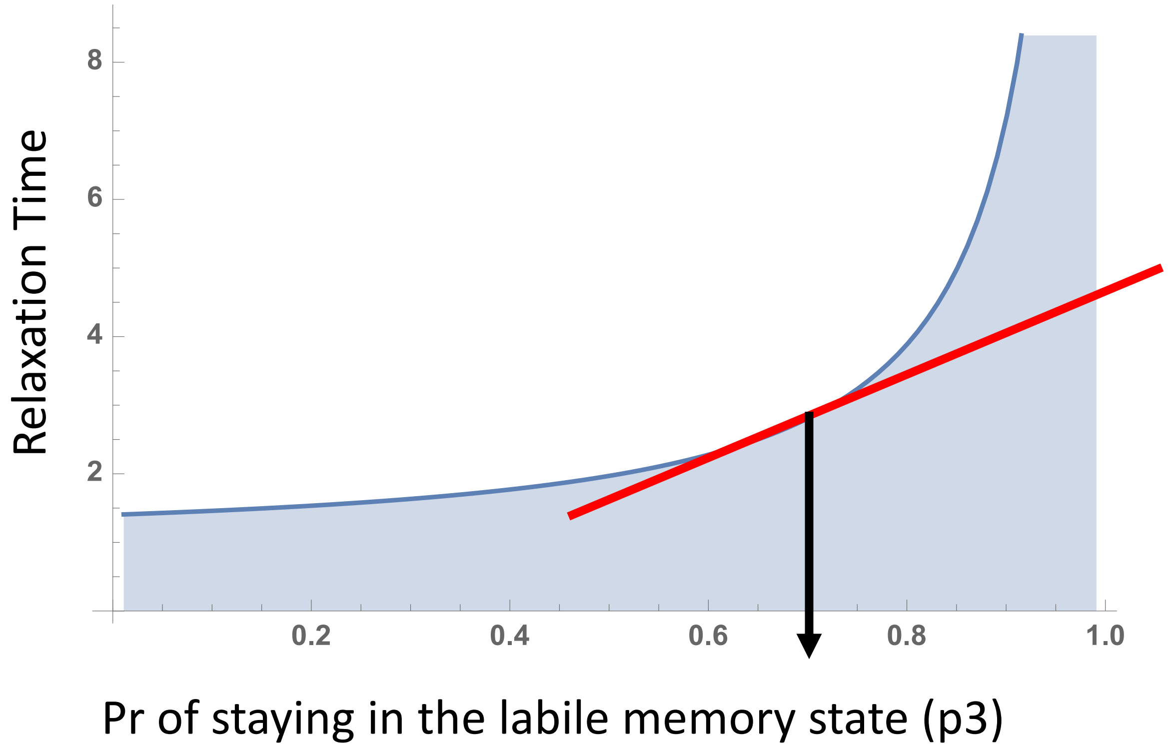
Square of the products must be less than the product of the squares (for memories to stay mixed)

Bounds on trauma: Cauchy-Schwarz Inequality

Upper bound on speed at which memories 'relax' into neutral state



Bounds on trauma: Cauchy-Schwarz Inequality



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

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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*

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Questions?