Deciphering Sleep Dynamics: Analyzing the Stages in Cannabis Users and Non-Users Using Fokker-Planck Equations

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Introduction

The brain ECS comprises a vast network of chemical signals and cellular receptors that are densely packed throughout our brains and bodies.

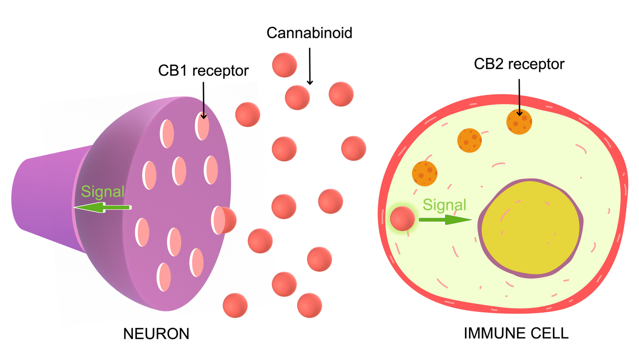

Figure 1. The endocannabinoid system (ECS) in a human brain.

Cannabis affects the ECS involved in regulating pain control, learning and memory, emotional processing, sleep, and eating.

How does cannabis affect sleep dynamics?

To contribute to this ogoing debate, we aim to solve a parameter optimization problem on a modified system of ODEs obtained via literature to match a wealth of hypnograms collected from both cannabis users and non-users.

A three-stage sleep-waking model

To study the dynamics of the three sleep stages in rats, the following nonlinear differential equations system was proposed in [1]:

$$\begin{aligned} \dot{a} &= -\alpha_0 a + \beta_0 ar \\ \dot{r} &= \alpha_1 r - \beta_1 ar \\ \dot{n} &= -\alpha_2 (n-5.5)^3 - \beta_2 ar \end{aligned} \tag{1}$$

where a, r, and n are the neuronal populations activities (firing rate) corresponding to the awake, REM and NREM sleep stages respectively.

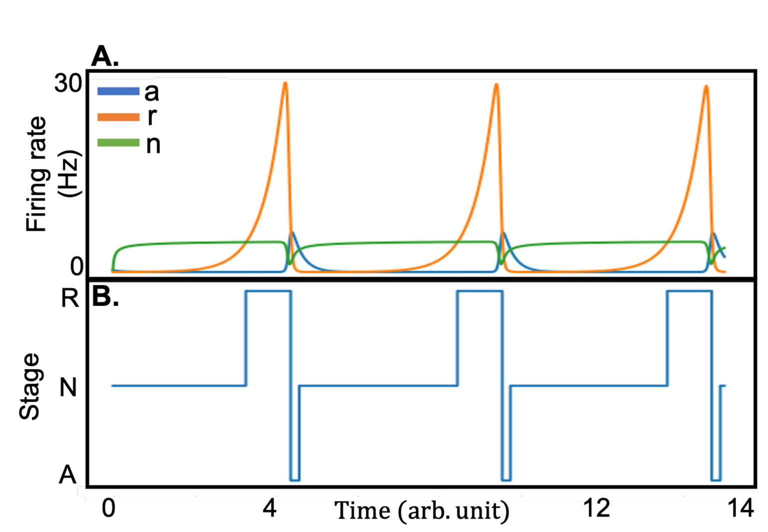

Figure 2. A. Simulations of Eq 1 with parameters $\alpha_0 = 4, \alpha_1 = 2, \alpha_2 = 1, \beta_0 = 1, \beta_1 = 4, \beta_2 = 1$ obtained by empirical methods.

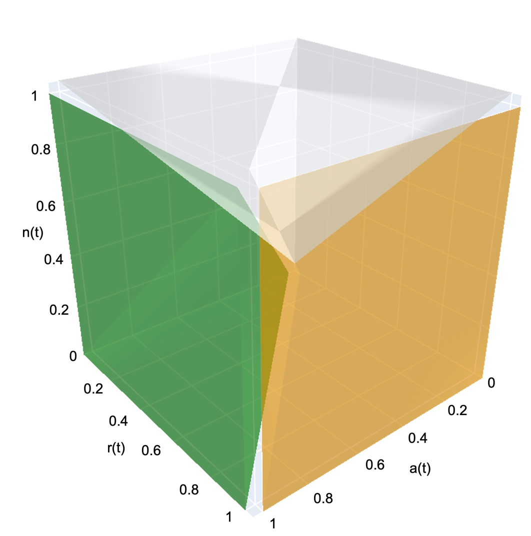

Figure 3. Geometry of the WTA strategy (Eq (2)).

An automated parameter estimation method using NCG

To align with experimental data, parameters were chosen (Fig 2), and white Gaussian noise was introduced in Eq(1). Given the challenges of estimating parameters from hypnograms due to their variability, we propose a parameter estimation method that represents the stocastic ODEs inspired by [1] via the Fokker-Planck equations and solves a parameter estimation problem using the non-linear conjugate gradient (NCG) method ([2]).

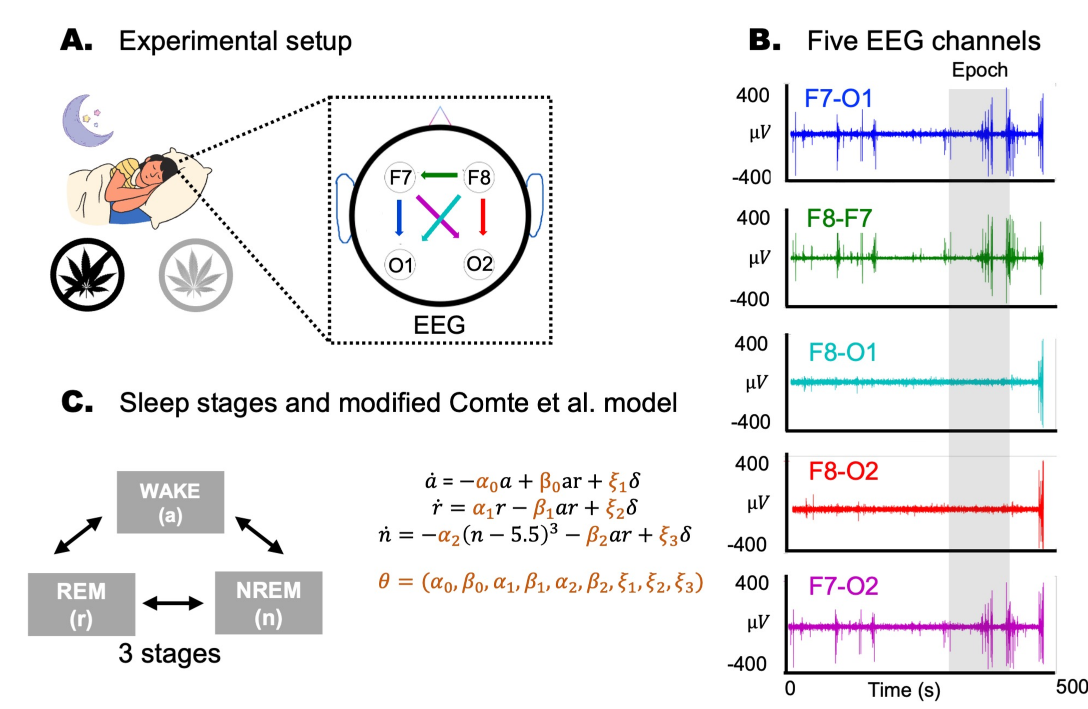

Figure 4. A. Subjects wear a nightly headband recording EEG and hypnogram data. B. The five EEG channels used to collect the data. C. Sleep stage transitions in a night as recorded by a hypnogram, and the modified system of Comte et al's model representing the dynamics of sleep stages.

Winner-Takes-All (WTA)

The following strategy was applied in obtaining the hypnogram from the simulations of Eq(1).

$$\begin{aligned} (a>r)\&(a>n) &\implies H = A \\ (r>a)\&(r>n) &\implies H = R \\ (n>a)\&(n>r) &\implies H = N \end{aligned} \tag{2}$$

where A, R, N denote the given vigilance state and H denotes the vigilance state output variable.

Optimization of deterministic system

We propose the following optimization problem.

$$\min_{\vec{\theta}\in T_{ad}} \frac{\alpha}{2}\int_\Omega \left[\phi - \phi^d\right]^2 \, dt + \frac{\gamma}{2}(\|\vec{\theta}\|)^2,$$

subject to

$$\begin{aligned} \dot{a} &= -\alpha_0 a + \beta_0 ar + \xi_1\delta \\ \dot{r} &= \alpha_1 r - \beta_1 ar + \xi_2\delta \\ \dot{n} &= -\alpha_2 (n-5.5)^3 - \beta_2 ar + \xi_3\delta, \\ a(0) &= a_0, r(0) = r_0, n(0) = n_0. \end{aligned} \tag{3}$$

where $\vec{\theta} = (\alpha_0, \alpha_1, \alpha_2, \beta_0, \beta_1, \beta_2, \xi_1, \xi_2, \xi_3)$, δ: cumulative cannabis intake of the subject, $\phi = \phi(a,r,n)$: a smoothed WTA (Eq 4), and ϕ^d: the experimental hypnogram.

Let $H_s(x) = \frac{1+\tanh(kx)}{2}$. Then we let

$$\phi(a,r,n) = \begin{bmatrix} H_s(a-r)H_s(a-n) \\ H_s(r-a)H_s(r-n) \\ H_s(n-a)H_s(n-r) \end{bmatrix} \tag{4}$$

Solving the forward equations, adjoint equations and the optimality conditions for Eq (3) with $\delta = 0$, initial guesses $\vec{\theta} = (\alpha_0 = 4; \beta_0 = 1.1, \xi_1 = 0, \alpha_1 = 2, \beta_1 = 4.1, \xi_2 = 0, \alpha_2 = 1, \beta_2 = 2.2, \xi_3 = 0)$, the NCG method successfully solves the parameter estimation for synthetic data Fig (5).

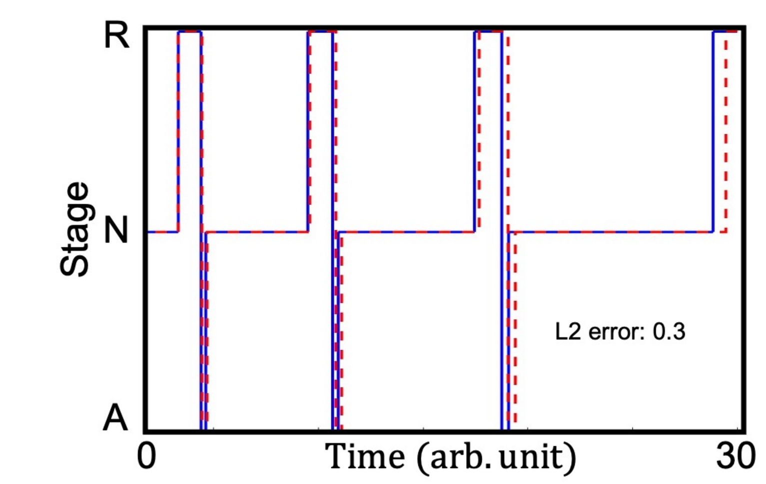

Figure 5. Comparision of the hypnogram obtained via solving Eq (3) for parameters via NCG (blue) and the hypnogram obtained via synthetic data from Eq (3) (red).

Navigating Stochasticity: Fokker-Planck Equations

Adding noise to Eq (3) results in

$$\begin{aligned} da &= [f_1(a,r,n,\vec{\theta})]dt + \sigma_1(a)dw_1 \\ dr &= [f_2(a,r,n,\vec{\theta})]dt + \sigma_2(r)dw_2 \\ dn &= [f_3(a,r,n,\vec{\theta})]dt + \sigma_3(n)dw_3 \end{aligned} \tag{5}$$

where $\sigma_1(a)dw_1, \sigma_2(r)dw_2$ and $\sigma_3(n)dw_3$: positive noise discretizations, dw_1, dw_2 and dw_3: IID Weiner noise distributions.

Let $X(t) = (a(t), r(t), n(t))$ then Eq (5) can be written as

$$dX(t) = F(X,\vec{\theta})dt + \sigma(X)d\vec{w}(t), X(0) = X_0 \tag{6}$$

which is a multidimensional stochastic differential equation. Here, $\sigma(X)$ is the diagonal matrix with $\sigma_1, \sigma_2, \sigma_3$ as its diagonal elements. Let $x = (a,r,n)$.

We now formulate the minimization problem:

$$\begin{aligned} &\min_{(\vec{\theta},\sigma)\in T_{ad}} \frac{\alpha}{2}\int_\Omega [\phi(x) - \phi^e]^2 \, dx + \frac{\beta}{2}\int_\Omega \sigma_1^2(x) + \sigma_2^2(x) + \sigma_3^2(x) \, dx \\ &\quad + \frac{\gamma}{2}(\|\vec{\theta}\|^2), \\ &\text{subject to} \\ &\quad \frac{\partial f}{\partial t} + \nabla\cdot(Ff) = \frac{\sigma_1^2}{2}\frac{\partial^2 f}{\partial x_1^2} + \frac{\sigma_2^2}{2}\frac{\partial^2 f}{\partial x_2^2} + \frac{\sigma_3^2}{2}\frac{\partial^2 f}{\partial x_3^2}, \ (x,t)\in\Omega\times(0,T), \\ &\quad f(x,0) = f_0(x), \ x\in\Omega. \end{aligned} \tag{7}$$

and aim to estimate the parameters $\vec{\theta}$ using NCG. Here, $f = f(x,t) = \mathbb{P}(X(t) = x(t)), \Omega \subset (\mathbb{R}^+)^3$, T_{ad}: admissible set for the parameters.

Future work

1. Apply the NCG method to deterministic ODEs (Eq (3)) and obtain the best parameters for experimental hypnograms.
2. Solve the optimization problem (Eq (7)), thereby obtaining an automated method of estimating parameters for the stochastic sleep dynamical system for the cannabis users and healthy control.

References

[1] J. C. Comte, M. Schatzman, P. Ravassard, P. H. Luppi, and P. A. Salin. A three states sleep-waking model. *Chaos Solitons and Fractals*, 29(4):808–815, August 2006.

[2] Pan Z. Roy, S. and S. Pal. A Fokker–Planck feedback control framework for optimal personalized therapies in colon cancer-induced angiogenesis. *J. Math. Biol.*, 84(23), 2022.