Nonparametric estimation of blood alcohol concentration from transdermal alcohol measurements using alcohol biosensor devices

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In collaboration with:

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- Used primarily for monitoring sobriety.

SCRAM CAM

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- Recently NIAAA called for research to construct alcohol biosensor devices which are more accurate, discreet, precise, and tamper proof.

SCRAM CAM

BACtrack Skyn

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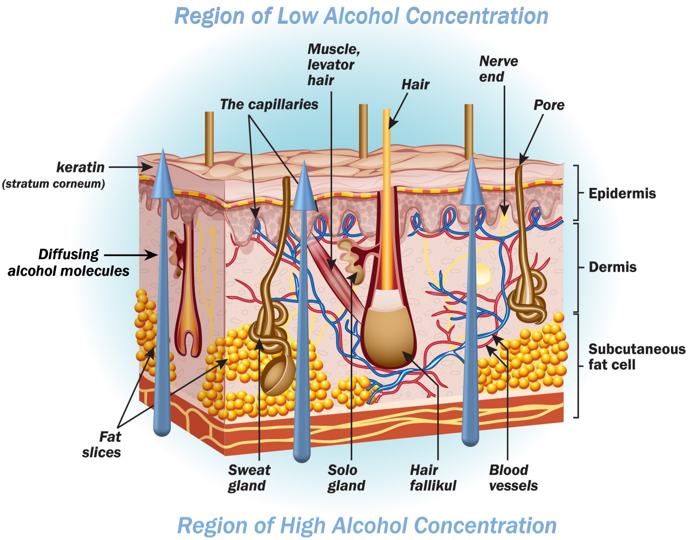
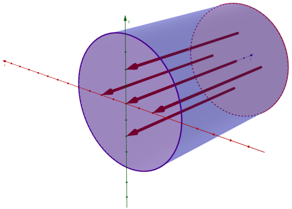

Region of Low Alcohol Concentration
Muscle, levator hair
Nerve end
Hair
The capillaries
Pore
keratin
(stratum corneum)
Epidermis
Diffusing alcohol molecules
Dermis
Subcutaneous fat cell
Fat slices
Sweat gland
Solo gland
Hair fallikul
Blood vessels
Region of High Alcohol Concentration

The Heat Equation

Definition of Variables

$u(\eta, t)$	- concentration of alcohol in moles/cm^2
$y(\eta, t)$	- concentration of alcohol in moles/cm^2 including biological variation $\varepsilon \sim N(0, \sigma)$
η	- depth into dermal layer (normalized as percentage of depth)
t	- time in hours
q	- parameters of diffusivity vector in cm^2/hour
$\alpha(t)$	- input of alcohol into the system at the bottom of the dermal layer ($\eta = 1$) in BAC/BrAC units



The Heat Equation: Two Parameters

Heat Equation in Strong Formulation

$$\frac{\partial u}{\partial t}(\eta, t) = q_1 \frac{\partial^2 u}{\partial \eta^2}(\eta, t), \qquad 0 < \eta < 1, t > 0 \qquad (1)$$

$$u(\eta, 0) = 0, \qquad 0 < \eta < 1 \qquad (2)$$

$$u(0, t) = q_1 \frac{\partial u}{\partial \eta}(0, t), \qquad t > 0 \qquad (3)$$

$$\frac{q_1}{q_2} \frac{\partial u}{\partial \eta}(1, t) = \alpha(t), \qquad t > 0 \qquad (4)$$

$$y(\eta, t) = c \cdot u(\eta, t) + \varepsilon, \qquad \varepsilon \sim N(0, \sigma) \qquad (5)$$

$$q = \langle q_1, q_2 \rangle \sim F \qquad (6)$$

Problem

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Discretizing the Heat Equation

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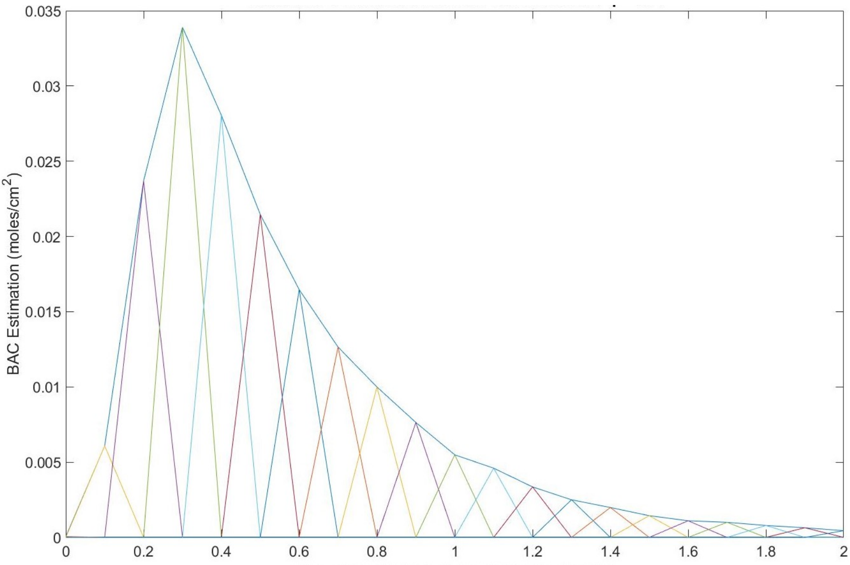
- Note: we sample from from two distributions to provide values for q at this stage, however much of the remainder of the project is concerned with estimating an appropriate value.

Plan to Solve this Problem

- Use the **Finite Element Method** with **B-Splines** to **discretize** η and t and view $u(\eta, t)$ as a matrix of concentration values.

B-Splines



BAC Estimation (moles/cm^2)
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2

The Final Discretized Model

Recursion With Respect to Time

Note: this vector is now only dependent on the parameter q.

$$\hat{u}^N(t_j; q) = \sum_{k=1}^{j} \left(\alpha_{k-1} \left(\hat{A}(q) \right)^{j-k} \right) \hat{B}(q)$$

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The Discretized Matrix Form

Note: this matrix is now only dependent on the parameter q.

$$U^{N,T}(q) = \left[\vec{0}, \left\{ \sum_{k=1}^{j} \left(\alpha_{k-1} \left(\hat{A}(q) \right)^{j-k} \right) \hat{B}(q) \right\}_{j=1}^{T} \right]$$

The Discretized Form at $\eta = 0$ (TAC) Depth

$$y(q) = \hat{c}(q) \cdot U^{N,T}(q)$$

TAC With Measurement Error

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$$y(q) = \hat{c}(q) \cdot U^{N,T}(q)$$

TAC with Measurement Error

$$y_\epsilon(q) = y(q) + \epsilon$$
$$\epsilon \sim N(0, \sigma)$$

Pairs of Probability Density Functions

Pair 1: $q_1 \sim \mathcal{N}(1, \sigma^2)$
$q_2 \sim \mathcal{N}(1, \sigma^2)$

Simulated TAC using Matlab

Pairs of Probability Density Functions

Pair 1:

$$q_1 \sim \mathcal{N}(1, \sigma^2)$$
$$q_2 \sim \mathcal{N}(1, \sigma^2)$$

Pair 2:

$$q_1 \sim 0.7\mathcal{N}(0.7, \sigma^2) + 0.3\mathcal{N}(1, \sigma^2)$$
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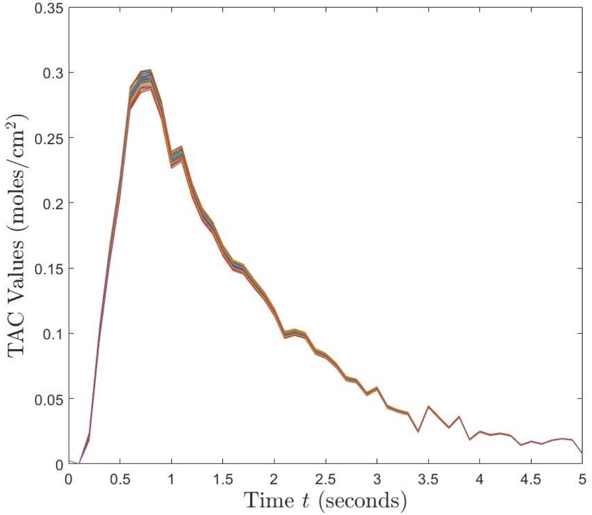
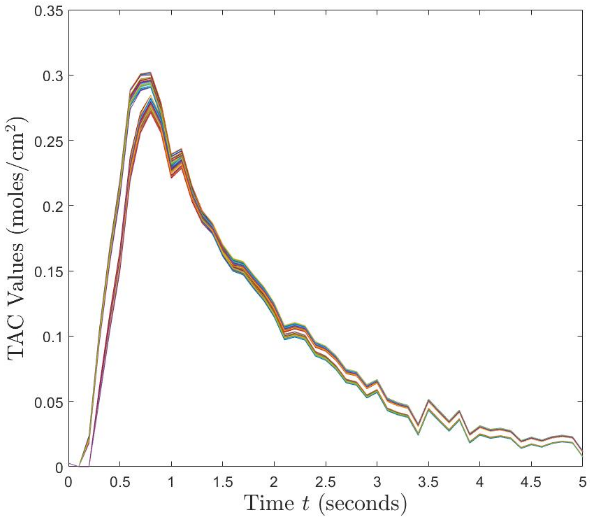
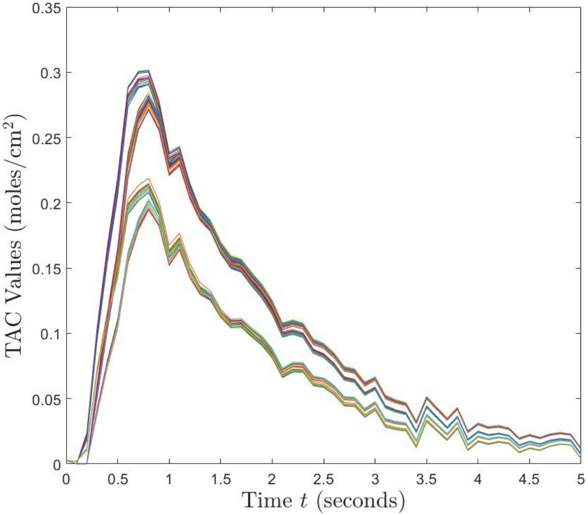
Pair 1: Simulated TAC using Matlab



Pair 2: Simulated TAC using Matlab



Pair 3: Simulated TAC using Matlab



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Likelihood Function

Let $Y_1, Y_2, \dots, Y_P$ be independent measurements that have a joint distribution $p(Y_1, Y_2, \dots, Y_P | q)$. The parameters are unknown random variables distributed with distribution F which is also unknown. For a given F parameter the **log likelihood function** is

$$\begin{aligned}\ell(F) = \log(p(Y_1, Y_2, \dots Y_P | F)) &= \log\left(\prod_{i=1}^{P} p_i(Y_i | F)\right) \\ &= \sum_{i=1}^{P} \log(p_i(Y_i | F)) \\ &= \sum_{i=1}^{P} \log\left(\int_{\Omega} p_i(Y_i | q)\, \mathrm{d}F(q)\right).\end{aligned}$$

Maximum Likelihood Estimation

Observe that when

$$L(F^*) \geq L(F)$$

for all $F \in \mathscr{F}$, then the **maximum likelihood estimator** F^{ML} is more likely to be F^* than any other F.

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Maximum Likelihood Estimator

The **maximum likelihood estimator** of F is

$$F^{ML} = \text{argmax}\{\ell(F) : F \in \mathscr{F}\}$$

where $\mathscr{F}$ is the family of all probability distributions on Ω.

Theorem: (Lindsay, 85)

If Ω is compact, F^{ML} can be found in the class of discrete distributions on Ω with at most P support points.

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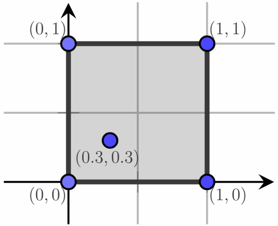
Carathéodory's Theorem: (Roberts, 73)

If $U \subseteq \mathbb{R}^n$ and its convex hull $H(U)$ has dimension m, then for each $z \in H(U)$, there exists $m+1$ points $x_0, x_1, \ldots, x_m$ of U such that z is a convex combination of these points.



Expectation-Maximization Optimization Problem

Maximum Likelihood Estimator

$$F^{ML} = \operatorname{argmax}\left\{\sum_{i=1}^{P}\log\left(\sum_{k=1}^{K} w_k p_i(Y_i \mid \xi_k)\right), K \leq P\right\}$$

$$w_k = \mathbb{P}(q = \xi_k) \geq 0, \text{ for all } 1 \leq k \leq K,$$

$$\sum_{k=1}^{K} w_k = 1$$

What is Needed For the Optimization Problem?

Let

$$\lambda = (\xi^K, w^K) = (\xi_1, \xi_2, \ldots, \xi_K, w_1, w_2, \ldots, w_K)$$

be the vector of weights and supports. It is now appropriate to state the question as

$$\ell(F) \approx \ell(\lambda) = \ell(\xi_1, \xi_2, \ldots, \xi_K, w_1, w_2, \ldots, w_K).$$

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NPAG Algorithm

Starting conditions: $\mathbf{Y}_\epsilon$, ξ^0, $\mathbf{a}$,$\mathbf{b}$,$\mathbf{\Delta_D}$

Output: $\xi, \mathbf{w}, \ell(\mathbf{w}, \xi)$

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Step 4: Check the exit condition for the log-likelihood difference, i.e. $\left|\ell(\lambda^{(n+1)}) - \ell(\lambda^{(n)})\right| \leq 10^{-4}$, and exit if true or else proceed to Step 5,

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Step 5: Expand the grid by adding new support points or reset the grid when support points are too close in proximity, go to Step 2.

D-Function

Define the D-Function, the directional derivative of $\ell(F)$ in the direction of the atomic density function δ_ξ, as

$$D(\xi, F) = \left(\sum_{i=1}^{P} \frac{p(Y_i \mid \xi)}{p(Y_i \mid F)} \right) - P. \tag{7}$$

Convergence of NPAG to F^{ML}

D-Function Properties

- $F^* = F^{ML}$ if and only if $\max_{\xi \in \Omega} D(\xi, F^*) = 0$.

Convergence of NPAG to F^{ML}

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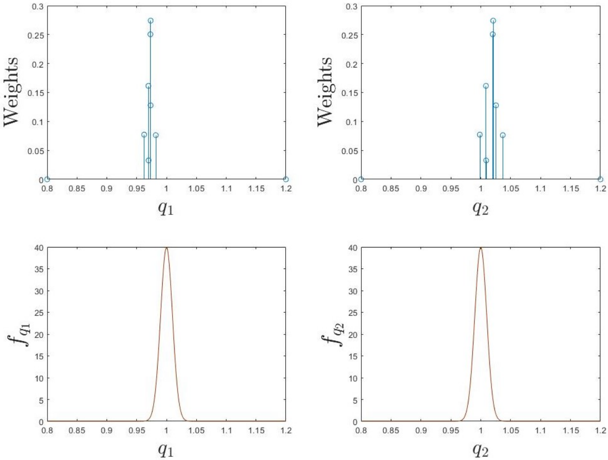
D-Function Properties

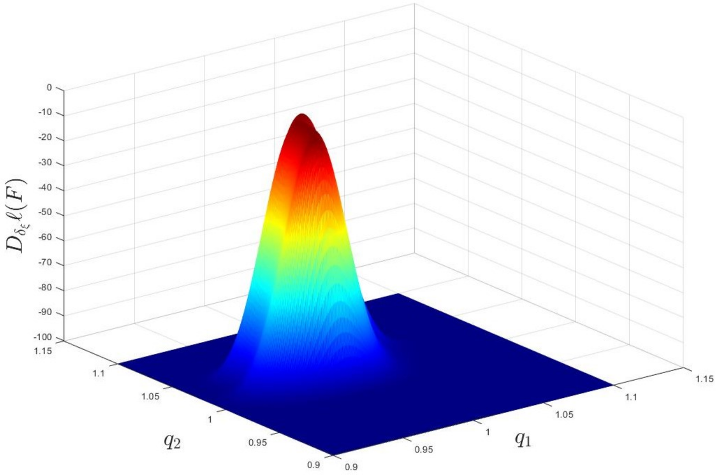
- $F^* = F^{ML}$ if and only if $\max_{\xi \in \Omega} D(\xi, F^*) = 0$.
- When $\max_{\xi \in \Omega} D(\xi, F^*) \neq 0$, it is true that

$$L(F^{ML}) - L(F^*) \leq \max_{\xi \in \Omega} D(\xi, F^*)$$

for $F^*, F^{ML} \in \mathscr{F}_K$.

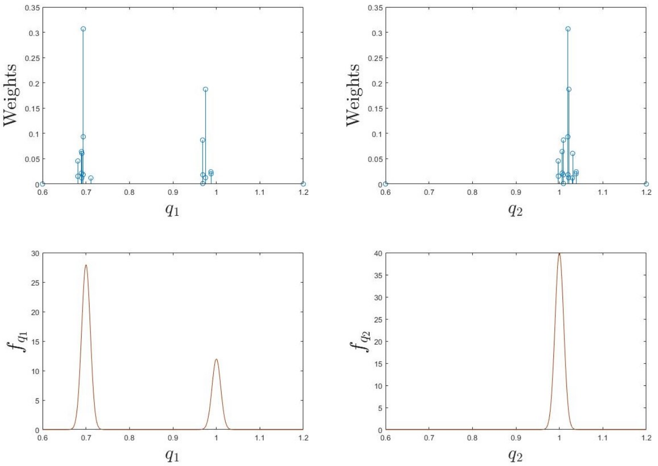


Weighted Mean: $q_1 = 0.9724$, $q_2 = 1.0183$



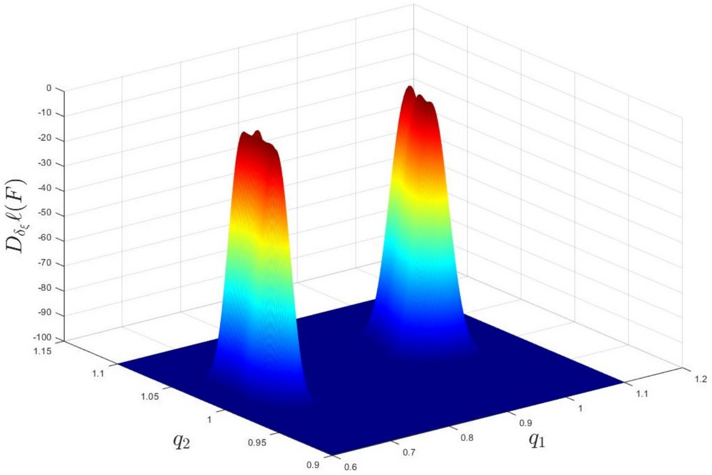
D-Function max $= -0.0019$

Pair 2: Maximum Likelihood using Matlab

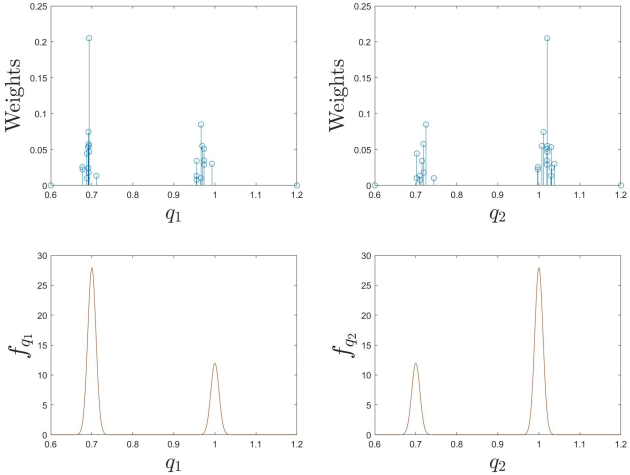


Weighted Mean: $q_1 = 0.7909$, $q_2 = 1.0183$

Pair 2: D-Function using Matlab

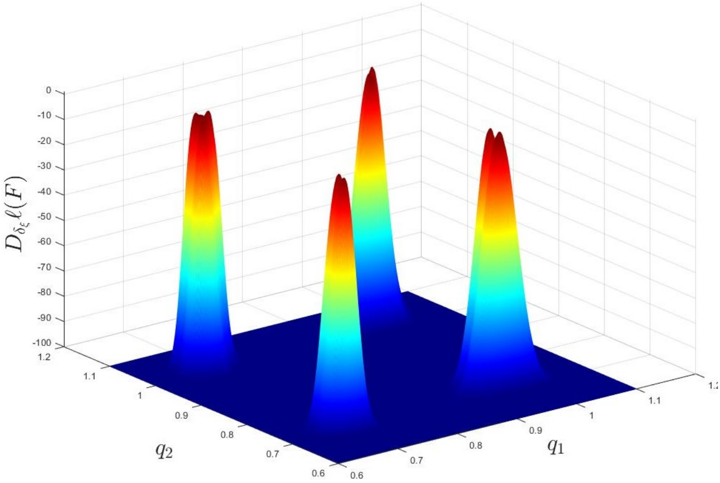


D-Function max $= -0.0026$



Weighted Mean: $q_1 = 0.7888$, $q_2 = 0.9343$

Pair 3: D-Function using Matlab



D-Function max = 0.0029

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Conclusions

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- A new diffusion model was developed and tested.
- Theory was established to reduce the maximum likelihood estimator to finite support.
- Simulated data tested and verified the model.
- The algorithm results for NPAG Algorithm are very encouraging and constitute further study.

Future Work

- Compare finite element method with B-splines against other discretization methods.

Future Work and Conclusions

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- Use a Bayesian approach to estimate the parameter for an individual.

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Acknowledgements

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my thesis committee,	**Dr. Jorge Garcia** and
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and our CalTech colleage	**Dr. Melike Sirlanci**

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Any Questions?

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