An inverse problem in the biology of olfactory cilia

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Joint work with

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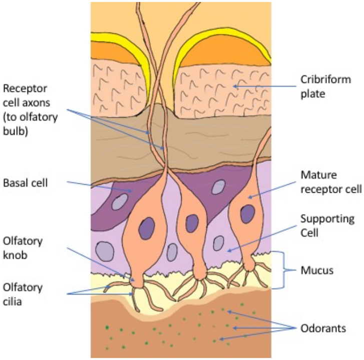
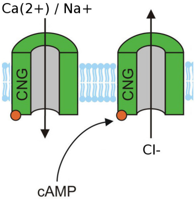
Transduction of olfactory signals

The molecular machinery that carries out this job is in the olfactory cilia



Structure and function of the olfactory epithelium

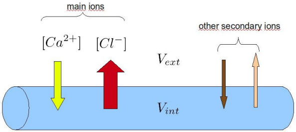


CNG ion channels through which depolarization of the neuron occurs, making it more positive charged, or less negative

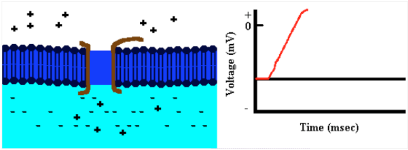
Olfactory mechanism

Depolarization of olfactory neurons

Electrical activity of ion exchange (main ions$\downarrow Ca^{2+}$, $\uparrow Cl^{-}$)



$\Delta V = V_{ext} - V_{int}$ = membrane difference potential

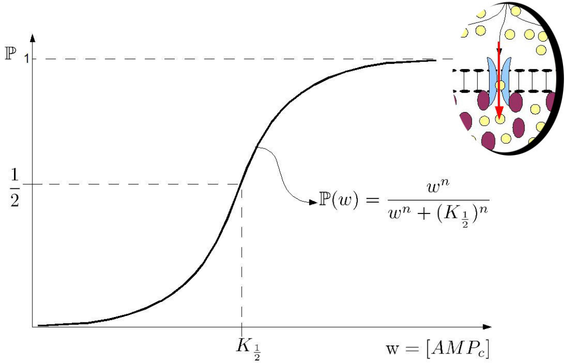


reference value of ΔV : $-40[mv]$

electrical activity during olfaction : $\pm 10[mv]$

Experimental measurement of the probability of opening for a CNG channel

$\mathbb{P}$ depends on the concentration ω of $[cAMP]$ by means of a Hill type-like function



Typical values for n are $n \simeq 2$

Outline

Mathematical Modelling Considerations

A Quick User's Guide to the Mellin Transform

Main Results

- A convolution equation
- A priori estimates : Continuity and observability inequalities
- Existence and uniqueness of ρ in a weighted $L^2 space$
- A pathological model : Non-existence of observability inequalities
- A non-stable identifiability result

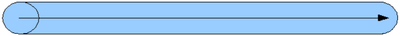
Numerics

Path Forward

Thanks

A difusion model for $\omega = [cAMP]$

$$\frac{\partial w}{\partial t} - D\frac{\partial^2 w}{\partial x^2} = 0$$

$w(t,0) = w_0$  $\frac{\partial w}{\partial x}(t,L) = 0$

$$w(0,x) = 0$$

Under the hypothesis of an infinitely long cilium, we have

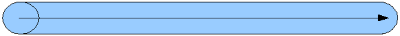
$$\omega(t,x) \simeq w(t,x) = \omega_0 \ \mathrm{erfc}\left(\frac{x}{2\sqrt{Dt}}\right)$$

where $\mathrm{erfc}(z) = 1 - \frac{2}{\sqrt{\pi}}\int_0^z e^{-\tau^2}\,d\tau$ (complementary error function).

An approximate explicit expression for ω

$$\frac{\partial w}{\partial t} - D\frac{\partial^2 w}{\partial x^2} = 0$$

$$w(t,0) = w_0$$



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A direct and an inverse problem

- Total average current as a function of ρ (direct problem)

$$\mathrm{I}[\rho](t) = \alpha_0 \int_0^L \rho(x)\mathbb{P}(w(t,x))dx$$

If $\mathbb{P}$ is smooth, the inverse problem is ill-posed

Proof.- The operator $\rho \mapsto \mathrm{I}[\rho]$ is compact from $L^p(0,L)$ into $L^p(0,T)$. Thus, $\rho \mapsto \mathrm{I}[\rho]$ cannot be at the same time injective with a left inverse continuous, because if so, then the identity map in $L^p(0,L)$ would be compact, which is knowingly false.

A direct and an inverse problem

- ρ as a function of the total average current (inverse problem)

$$\mathrm{I}[\rho](t) = \alpha_0 \int_0^L \rho(x)\mathbb{P}(w(t,x))dx$$

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A new inverse model

$\mathbb{P}$ is replaced by its following non-smooth version :

$$H(x) = \mathbb{P}(x)\,\mathbb{1}_{x \le a} + \mathbb{1}_{a < x \le \omega_0},$$

where a is a real parameter in $(0, \omega_0)$; imposed saturation level.

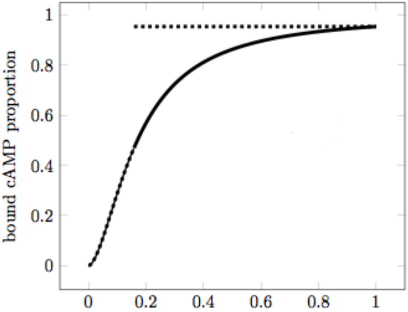

Figure: The Hill function $\mathbb{P}$ and its disruptive version H (dashed line)
$a = 0.157, \quad \omega_0 = .9, \quad \omega \in [0, \omega_0]$

A new inverse model

$\mathbb{P}$ is replaced by its following non-smooth version :

$$H(x) = \mathbb{P}(x)\,\mathbb{1}_{x \leq a} + \mathbb{1}_{a < x \leq \omega_0},$$

where a is a real parameter in $(0, \omega_0)$; imposed saturation level.

The new inverse model consists of finding $\rho = \rho(x) > 0$;

$$\forall t \geq 0, \qquad \mathrm{I}[\rho](t) = \alpha_0 \int_0^L \rho(x) H(w(t,x))dx$$

A quick user's guide to the Mellin transform

Definition

- For $q \in \mathbb{R}$, we denote $\quad q + i\mathbb{R} = \{q + it, t \in \mathbb{R}\}$
- For $p \in \mathbb{R}, p \geq 1$, we define

$$L^p([0,\infty), x^q) = \left\{ f : [0,+\infty) \to \mathbb{R} \mid \|f\|_{L^p_q} \overset{(\mathrm{def})}{=} \left(\int_0^\infty |f(x)|^p x^q dx \right)^{1/p} < +\infty \right\}$$

- Let f be in $L^1([0,\infty), x^q)$. The Mellin transform of f is a complex valued function defined on the vertical line $q + 1 + i\mathbb{R}$ by

$$\mathcal{M}f(s) \overset{(\mathrm{def})}{=} \int_0^\infty x^s f(x) \frac{dx}{x}$$

- Theorem #1

The Mellin transform is a linear continuous map from $L^1\left([0,\infty), x^q\right)$ into $\mathcal{C}^0(q+1+i\mathbb{R};\mathbb{C}) \hookrightarrow L^\infty(q+1+i\mathbb{R};\mathbb{C})$; its operator norm is 1.

- Main operational properties

function	**Mellin transform**
$f(at),\ a>0$	$a^{-s}\mathcal{M}f(s)$
$f(t^a),\ a\neq 0$	$\lvert a\rvert^{-1}\mathcal{M}f(a^{-1}s)$
$f^{(k)}(t)$	$(-1)^k(s-k)_k\mathcal{M}f(s-k)$

where, $\forall x\in\mathbb{R}\ \forall k\geq 1$ we write

$$(x)_k = x\cdots(x-k+1) = \prod_{j=0}^{k-1}(x-j)\ \text{(Pochhammer symbol)}$$

The Mellin multiplicative convolution

- For two functions f, g, the multiplicative convolution $(f * g)$ is

$$(f * g)(x) = \int_0^\infty f(y)\, g\left(\frac{x}{y}\right) \frac{dy}{y}$$

- Proposition $\#1$

$$\mathcal{M}(f * g)(s) = \mathcal{M}f(s)\, \mathcal{M}g(s),$$

whenever this expression is well defined.

Proof.- A careful and appropriate used of integration by parts.

Our inverse problem as a convolution equation

$$\forall t \geq 0 \qquad \mathrm{I}[\rho](t) = \int_0^L \rho(x) H(w(t,x))dx = \int_0^L \rho(x) H(\omega_0 \operatorname{erfc}(\frac{x}{2\sqrt{Dt}}))dx$$

Defining G as

$$G(z) = H\left(\omega_0 \operatorname{erfc}\left(\frac{1}{2\sqrt{Dz}}\right)\right)$$

we have $\mathrm{I}[\rho](t) = \int_0^L \rho(x) G(\frac{\sqrt{t}}{x})dx$. Thus, by extending ρ by zero to $[0, +\infty]$, and rescaling time t in t^2,

$$\mathrm{I}[\rho](t^2) = \int_0^\infty x\rho(x) G\left(\frac{t}{x}\right) \frac{dx}{x} = \Big(x\rho(x)\Big) * G$$

which is a convolution equation in $x\rho(x)$.

Our inverse problem as a convolution equation

Taking Mellin transform on both sides and using its operational properties, we formally obtain

$$\mathcal{M}G(s)\mathcal{M}\rho(s+1) = \mathcal{M}\left(\mathrm{I}[\rho](t^2)\right)(s) = \frac{1}{2}\mathcal{M}\mathrm{I}[\rho](s/2)$$

or equivalently,

$$(\star) \qquad \mathcal{M}\rho(s+1) = \frac{1}{2}\frac{\mathcal{M}\mathrm{I}[\rho]\,(s/2)}{\mathcal{M}G(s)}$$

- Plancherel's Identity

The Mellin transform extends, in a unique manner, to an isometry from $L^2\left([0,\infty), x^{2q-1}\right)$ into the classical $L^2(q+i\mathbb{R})$ space, i.e.,

$$\mathcal{M} \in \mathcal{L}\left(L^2_{2q-1}; L^2(q+i\mathbb{R})\right)$$

where L^2_{2q-1} is a short notation for $L^2\left([0,\infty), x^{2q-1}\right)$

Theorem#2

Let $a > 0$ and $r < 1$ be given. Assume that the Mellin transforms of ρ and $\mathrm{I}[\rho]$ satisfy $(\star)$.

- $\rho \in L^2([0,\infty), x^r) \Rightarrow \exists C > 0$ s.t.

$$\|\mathrm{I}[\rho]\|_{L^2([0,\infty),t^{\frac{r-3}{2}})} \leq C \|\rho\|_{L^2([0,\infty),x^r)}$$

  where $C = \sqrt{2}\sup_{s\in\frac{r-1}{2}+i\mathbb{R}} |\mathcal{M}G(s)| < +\infty$

- $\rho \in L^2([0,\infty), x^r)$ and a is small enough $\Rightarrow \exists C > 0$ s.t.

$$\left\|(\mathrm{I}[\rho])'\right\|_{L^2([0,\infty),t^{\frac{r+1}{2}})} \leq C \|\rho\|_{L^2_r}$$

  where $C = \sqrt{2}\sup_{s\in\frac{r-1}{2}+i\mathbb{R}} \left|\left(\frac{s}{2}\right)\mathcal{M}G(s)\right| < +\infty$

Existence and uniqueness of ρ in a weighted L^2*space*

Determination of a unique distribution of CNG ion channels

Theorem#3

Let $a > 0$ and $r < 1$ be given. Assume that the Mellin transforms of ρ and $\mathrm{I}[\rho]$ satisfy $(\star)$, i.e.

$$\mathcal{M}\rho(s+1) = \frac{1}{2}\frac{\mathcal{M}\mathrm{I}[\rho]\,(s/2)}{\mathcal{M}G(s)},$$

then

- If $\mathrm{I} \in L^2([0,\infty), t^{\frac{r-3}{2}})$, $\mathrm{I}' \in L^2([0,\infty), t^{2+\frac{r-3}{2}})$ and a is small enough, then $\exists!\ \rho \in L^2([0,\infty), x^r), \exists C > 0$ s.t.

$$\|\mathrm{I}\|_{L^2([0,\infty),t^{\frac{r-3}{2}})} + \|\mathrm{I}'\|_{L^2([0,\infty),t^{2+\frac{r-3}{2}})} \geq C\,\|\rho\|_{L^2_r}$$

where $C = \sqrt{2}\inf_{s\in\frac{r-1}{2}+i\mathbb{R}} \left|\left(\frac{s}{2}\right)\mathcal{M}G(s)\right| > 0$

Theorem#2 and #3, Sketch of the proof

Two main steps :

- Appropriate algebraic manipulation of $(\star)$ using operational properties of the Mellin transform
- Come back to the original variables using Plancherel's isometry

From $(\star)$ it follows that

$$\mathcal{M}\mathrm{I}[\rho](s) = 2\,\mathcal{M}G(2s)\,\mathcal{M}\rho(2s+1)$$

and hence,

$$(s-k)_k\,\mathcal{M}\mathrm{I}[\rho](s-k) = 2(s-k)_k\,\mathcal{M}G(2(s-k))\,\mathcal{M}\rho(2(s-k)+1)$$

Theorem#2 and #3, Sketch of the proof

- Come back to the original variables using Plancherel's isometry

As the Mellin transform is an isometry (up to the factor $1/\sqrt{2\pi}$) from L^2_{2q-1} onto $L^2(q+i\mathbb{R})$, for s in $q+i\mathbb{R}$ we have

$$\begin{aligned}
\left\|(\mathrm{I}[\rho])^{(k)}\right\|_{L^2_{2q-1}} &= \frac{1}{\sqrt{2\pi}}\left\|(-1)^k(s-k)_k\,\mathcal{M}\mathrm{I}[\rho](s-k)\right\|_{L^2(q+i\mathbb{R})}\\
&= \frac{2}{\sqrt{2\pi}}\left\|(s-k)_k\,\mathcal{M}G(2(s-k))\,\mathcal{M}\rho(2(s-k)+1)\right\|_{L^2(q+i\mathbb{R})}\\
&= \frac{2}{\sqrt{2\pi}}\left\|(s)_k\,\mathcal{M}G(2s)\,\mathcal{M}\rho(2s+1)\right\|_{L^2(q-k+i\mathbb{R})}\\
&= \frac{1}{\sqrt{\pi}}\left\|\left(\frac{s}{2}\right)_k\,\mathcal{M}G(s)\,\mathcal{M}\rho(s+1)\right\|_{L^2(2(q-k)+i\mathbb{R})}
\end{aligned}$$

Theorem#2 and #3, Sketch of the proof

- Come back to the original variables using Plancherel's isometry

As $\mathcal{M}$ is an isometry of $L^2\left(2(q-k)+1+i\mathbb{R}\right)$ onto $L^2_{4(q-k)+1}$, we have

$$\|\mathcal{M}\rho(s+1)\|_{L^2(2(q-k)+i\mathbb{R})} = \|\mathcal{M}\rho(s)\|_{L^2(2(q-k)+1+i\mathbb{R})} = \sqrt{2\pi}\,\|\rho\|_{L^2_{4(q-k)+1}}$$

Gathering together the above inequalities, the definitions of C_ℓ, C_u yield,

$$C_\ell\,\|\rho\|_{L^2_{4(q-k)+1}} \leq \left\|(\mathrm{I}[\rho])^{(k)}\right\|_{L^2_{2q-1}} \leq C_u\,\|\rho\|_{L^2_{4(q-k)+1}}$$

Taking $r = 4(q-k)+1$, that is $q = k + \frac{r-1}{4}$, provides the result.

Our original inverse problem as a convolution equation

$$\forall t \geq 0 \qquad \mathrm{I}[\rho](t) = \int_0^\infty \rho(x)\mathbb{P}(w(t,x))dx$$

Defining $\tilde{G}$ as

$$\tilde{G}(z) = \mathbb{P}\left(\omega_0 \,\mathrm{erfc}\left(\frac{1}{2Dz}\right)\right),$$

and rescaling time t in t^2, we obtain a convolution equation very similar to $(\star)$:

$$(\star\star) \qquad \mathcal{M}\rho(s+1) = \frac{1}{2}\frac{\mathcal{M}\mathrm{I}[\rho]\,(s/2)}{\mathcal{M}\tilde{G}(s)}$$

Stability and non-observability

Theorem#4

Let $r < 1$ be fixed.

- $\rho \in L^2([0,\infty), x^r) \Rightarrow \exists C > 0$ s.t.

$$\|\mathrm{I}[\rho]\|_{L^2([0,\infty), t^{\frac{r-3}{2}})} \leq C \|\rho\|_{L^2_r}.$$

- $\forall k \in \mathbb{N} \quad \nexists C_k \geq 0$ such that the observability inequality :

$$\left\|(\mathrm{I}[\rho])^{(k)}\right\|_{L^2([0,\infty), t^{2k+\frac{r-3}{2}})} \geq C_k \|\rho\|_{L^2_r},$$

holds for every function $\rho \in L^2([0,\infty), x^r)$.

Remark This result shows that $\mathrm{I} \in \mathcal{L}\left(L^2_r; L^2_{\frac{r-3}{2}}\right)$, and if the inverse problem is identificable (i.e, I is injective), then I^{-1} cannot be continuous, as shown by the second inequality below.

Identificability result without stability

Theorem#5

Let $r < 0$ and $\rho \in L^1([0,\infty), x^r)$ be arbitrary. We consider the operator $\mathrm{I}[\rho]$ defined by

$$\mathrm{I}[\rho](t) = \int_0^\infty \rho(x)\mathbb{P}(w(t,x))dx \qquad \forall t \geq 0$$

If there exists a non empty open set U of $(0,\infty)$ s.t.

$$\mathrm{I}[\rho](t) = 0 \quad \forall t \in U,$$

then $\rho = 0$ a.e. on $(0,\infty)$.

Proof.- Lebesgue's dominated convergence theorem for analytic functions allows us to prove that $\mathrm{I}[\rho]$ is analytic in $(0,+\infty)$.

Proof of Identifiability

Proof.- (cont.) As $\mathrm{I}[\rho]$ vanishes on U, the principle of permanence implies that it vanishes on the connected set $(0, +\infty)$, i.e.,

$$\forall t \in (0, +\infty) \quad \mathrm{I}[\rho](t) = 0$$

To conclude, we take here Mellin transform and use the

Lemma (Holomorphy and rapid decay of the Mellin transform)

Let $f \in \mathcal{S}_x[0, \infty)$. Its Mellin transform $\mathcal{M}f$ is holomorphic on the right half-plane, and it decays faster than any negative power of t over every vertical line, i.e.,

$$\forall q > 0 \; \forall k \in \mathbb{N} \; \exists C \geq 0 \; s.t.$$
$$|\mathcal{M}f(q + it)| \leq C \, \frac{1}{t^k} \quad \forall t \in \mathbb{R}$$

Measured current is a sigmodial function with short delay,

similar to the profiles in some applications (Chen et al., *BioPhysical J.* **76**, 1999)

$$\mathrm{I}(t) = \begin{cases} 0 & t \in (0, t_{Delay}) \\ \mathrm{I}_{\mathrm{Max}} \left[1 + \left(\dfrac{K_{\mathrm{I}}}{t - t_{Delay}} \right)^{n_{\mathrm{I}}} \right]^{-1} & t > t_{Delay}, \end{cases}$$

with $t_{Delay} = 30ms$, $n_{\mathrm{I}} \simeq 2.2$, $\mathrm{I}_{Max} = 150pA$ and $K_{\mathrm{I}} \simeq 100ms$.

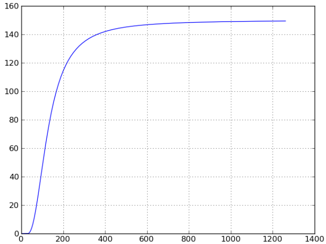

Figure: $\mathrm{I}(t)$, a sigmodial function

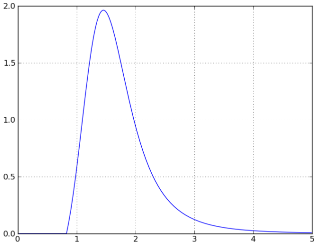

Figure: Numerical reconstruction of ρ

Path forward

- More accurate numerical simulations, a stronger validation of the inverse mathematical model

Thank You for your Attention !