Modelling our sense of smell

by

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What are olfactory cilia?

The nasal epithelium (mucous) is the part of the nose which traps smells and communicates them to the brain. The microscopic olfactory cilia play an important role in the perception of smell.
Experimental procedure developed by S. J. Kleene & collaborators around 1994
Mechanism of depolarization induced by the presence of pheromones on the ciliary membrane.
Olfactory mechanism

Depolarization of olfactory neurons

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

Reference value of $\Delta V$: $-40[mv]$

Electrical activity during olfaction: $\pm 10[mv]$
Experimental measurement of the probability of opening for a CNG channel \( \mathbb{P} \) depends on the concentration \( \omega \) of [cAMP] by means of a Hill type-like function

Hill function of exponent \( n > 0 \). It is defined by:

\[
\forall \omega \geq 0 \quad \mathbb{P}(\omega) := \frac{\omega^n}{\omega^n + K_1^{n/2}}.
\]

where \( K_1^{1/2} > 0 \) represents the half-bulk concentration and \( n \) the average number of bound molecules when a CNG ion channel opens; Typical values for \( n \) are \( n \approx 2 \)

The disrupted version of \( \mathbb{P} \) is defined by:

\[
\mathbb{H}(\omega) = \mathbb{P}(\omega) \mathbb{1}_{\omega \leq a} + \mathbb{1}_{a < \omega < +\infty}
\]

(dashed line), where \( a \) is a real parameter; imposed saturation level (\( a = K_1^{1/2} > 0 \) in this example).
Mathematical Modelling Considerations

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

\[
\frac{\partial \omega}{\partial t} - D \frac{\partial^2 \omega}{\partial x^2} = 0
\]

Notations

- $L$: Length of a single cilium
- $\rho = \rho(x)$: density of CNG channels along the ciliar membrane
- $I = I(t) = I[\rho](t)$: Total average electrical current at time $t$

An integral equation model: Total average current as a function of $\rho$

\[
I[\rho](t) = \alpha_0 \int_0^L \rho(x) H(\omega(t, x)) \, dx
\]
Mathematical Modelling Considerations

An integral equation model

\[ \frac{\partial \omega}{\partial t} - D \frac{\partial^2 \omega}{\partial x^2} = 0 \]

\[ \omega(t, 0) = \omega_0 \]

\[ \omega(0, x) = 0 \]

\[ \frac{\partial \omega}{\partial x}(t, L) = 0 \]

Notations

- \( L \): Length of a single cilium
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- \( I = I(t) = I[\rho](t) \): Total average electrical current at time \( t \)

An integral equation model: Total average current as a function of \( \rho \)

\[ I[\rho](t) = \alpha_0 \int_0^L \rho(x) H(\omega(t, x)) \, dx \]
Mathematical Modelling Considerations

Under the hypothesis of an infinitely long cilium, we have

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

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

A simplified integral equation model

$$I[\rho](t) = \alpha_0 \int_0^{+\infty} \rho(x) H(c(t, x)) dx$$

Pour en savoir plus

Our inverse problem

It consists in recovering the distribution of CNG ions channels from measurements of the total average current, through the above integral equation model

\[ I[\rho](t) = \alpha_0 \int_0^{+\infty} \rho(x) H(c(t, x)) \, dx \]

where

\[ c(t, x) = \omega_0 \text{erfc} \left( \frac{x}{2\sqrt{Dt}} \right) \]
A quick user’s guide to the Mellin transform

Definition

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

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

- 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

\[
\mathcal{M}f(s) \overset{(\text{def})}{=} \int_0^\infty x^s f(x) \frac{dx}{x}
\]
A quick user’s guide to the Mellin transform

Basic user’s operational properties

• Proposition #1

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

• Main operational properties

<table>
<thead>
<tr>
<th>function</th>
<th>Mellin transform</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f(at), \ a &gt; 0$</td>
<td>$a^{-s} \mathcal{M}f(s)$</td>
</tr>
<tr>
<td>$f(t^a), \ a \neq 0$</td>
<td>$</td>
</tr>
<tr>
<td>$f^{(k)}(t)$</td>
<td>$(-1)^k (s - k)_k \mathcal{M}f(s - k)$</td>
</tr>
</tbody>
</table>

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

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

**Proposition #2**

If \( f \in L^1([0, \infty), x^q) \land \mathcal{M}f \in L^1(q + 1 + i\mathbb{R}) \) then one can define

\[
\mathcal{M}^{-1}_q f(x) = \frac{1}{2\pi} \int_{\mathbb{R}} f(q + it)x^{-(q+it)}dt,
\]

and the following inversion identity holds true:

\[
f(x) = \left[ \mathcal{M}^{-1}_{q+1}(\mathcal{M}f) \right](x) \quad \text{for a.e. } x \text{ in } [0, \infty)
\]
The Mellin multiplicative convolution

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

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

- Proposition #3

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

  whenever this expression is well defined.

Proof.- A careful and appropriate used of integration by parts.
The inverse problem as a convolution equation

Once $\rho$ has been extended by zero to $[0, +\infty)$, we have

$$\forall t \geq 0 \quad I[\rho](t) = \int_{0}^{+\infty} \rho(x) \mathbb{H}(w(t, x)) \, dx = \int_{0}^{+\infty} \rho(x) \mathbb{H} \left( \omega_0 \operatorname{erfc} \left( \frac{x}{2\sqrt{Dt}} \right) \right) \, dx$$

Defining $G$ as

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

we have $I[\rho](t) = \int_{0}^{L} \rho(x) G\left( \frac{\sqrt{t}}{x} \right) \, dx$. Thus, rescaling time $t$ in $t^2$,

$$I[\rho](t^2) = \int_{0}^{\infty} x\rho(x) G\left( \frac{t}{x} \right) \frac{dx}{x} = \left( x\rho(x) \right) * G$$

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

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The inverse problem as a convolution equation

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

\[ MG(s)M \rho(s + 1) = M \left( I[\rho](t^2) \right)(s) = \frac{1}{2} MI[\rho](s/2) \]

or equivalently,

\[ (*) \quad M \rho(s + 1) = \frac{1}{2} \frac{MI[\rho](s/2)}{MG(s)} \]

- Plancherel’s Identity

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

\[ \mathcal{M} \in \mathcal{L}(L^2([0, \infty), x^{2q-1}) ; L^2(q + i\mathbb{R})) \]
Existence & uniqueness of $\rho$ in weighted $L^2$ spaces

https://doi.org/10.1051/m2an/2017062

Theorem #1 ($\exists!$ distribution of CNG ion channels)

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

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

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

where $C = \sqrt{2} \inf_{s \in \frac{r-1}{2} + i\mathbb{R}} \left| \left( \frac{s}{2} \right) \mathcal{M}_G(s) \right| > 0$. 
A priori estimates
The proof of Theorem#1 is based in the following general a priori estimates, and several technical lemmas providing sharp estimates from above and from below of $\mathcal{M}G(s)$; Th.Bourgeron et al., loc. cit. for details)

Lemma#2 (General continuity and observability inequalities)
Let $k = 0$ or 1 and $r \in \mathbb{R}$ be arbitrary. Assume that the Mellin transforms of $\rho$ and $I[\rho]$ satisfy $\mathcal{M}$, i.e.

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

then

$$C^k_{\ell} \|\rho\|_{L^2_r} \leq \left\| (I[\rho])^{(k)} \right\|_{L^2_{2k + r - 3/2}} \leq C^k_u \|\rho\|_{L^2_r},$$

where

$$C^k_{\ell} = \sqrt{2} \inf_{s \in \frac{r-1}{2} + i\mathbb{R}} \left| \left( \frac{s}{2} \right)^k \mathcal{M}G(s) \right| > 0, \quad C^k_u = \sqrt{2} \sup_{s \in \frac{r-1}{2} + i\mathbb{R}} \left| \left( \frac{s}{2} \right)^k \mathcal{M}G(s) \right| < +\infty.$$
Sketch of the proof of the a priori estimates

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

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

and hence,

\[
(s - k)_k \mathcal{M}\text{I}[\rho](s - k) = 2(s - k)_k \mathcal{M}\text{G}(2(s - k)) \mathcal{M}\rho(2(s - k) + 1)
\]
Sketch of the proof of the a priori estimates

- 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 $L^2(q+i\mathbb{R})$, we have

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

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

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

$$
= \frac{1}{\sqrt{\pi}} \left\| \left( \frac{s}{2} \right)_k \mathcal{M}G(s) \mathcal{M}\rho(s + 1) \right\|_{L^2(2(q-k)+i\mathbb{R})}
$$
Sketch of the proof of the a priori estimates

Come back to the original variables using Plancherel’s isometry

As $\mathcal{M}$ is an isometry of $L^2(2(q - k) + 1 + i\mathbb{R})$ 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 $C_\ell, C_u$ yield,

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

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

Why is a model with the full Hill function not realistic?

\[ I[\rho](t) = \alpha_0 \int_0^{+\infty} \rho(x) \mathbb{P}(c(t, x)) \, dx \]

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

Proof.- The operator \( \rho \mapsto I[\rho] \) is compact from \( L^p(0, L) \) into \( L^p(0, T) \), for every \( L, T > 0, 1 < p < \infty \). Thus, \( \rho \mapsto I[\rho] \) cannot be at the same time injective with a left inverse continuous (even if \( I \) is injective, its inverse would not be continuous), because if so, then the identity map in \( L^p(0, L) \) would be compact, which is knowingly false.
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The full Hill function inverse problem as a convolution equation

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

Defining \( \tilde{G} \) as

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

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

\[ (\star\star) \quad \mathcal{M}\rho(s + 1) = \frac{1}{2} \frac{\mathcal{M}I[\rho](s/2)}{\mathcal{M}\tilde{G}(s)} \]
Stability and non-observability

Theorem #3
Let $r < 1$ be fixed.

- $\rho \in L^2([0, \infty), x^r) \Rightarrow \exists C > 0$ s.t.
  \[
  \|I[\rho]\|_{L^2([0, \infty), t^{\frac{r-3}{2}})} \leq C \|\rho\|_{L^2_r}. 
  \]

- $\forall k \in \mathbb{N}$ $\nexists C_k \geq 0$ such that the observability inequality:
  \[
  \left\| (I[\rho])^{(k)} \right\|_{L^2([0, \infty), t^{2k+\frac{r-3}{2}})} \geq C_k \|\rho\|_{L^2_r},
  \]
  holds for every function $\rho \in L^2([0, \infty), x^r)$.

Remark  
This result shows that $I \in \mathcal{L}\left(L^2_r; L^2_{\frac{r-3}{2}}\right)$, and if the inverse problem is identifiable (i.e, $I$ is injective), then $I^{-1}$ cannot be continuous, as shown by the second inequality below.
Identifiability result without stability

Theorem #4

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

$$I[\rho](t) = \int_0^\infty \rho(x) P(c(t, x)) dx \quad \forall t \geq 0$$

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

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

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

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

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

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

To conclude, we take here Mellin transform and use the Lemma#5 (Holomorphy and rapid decay of the Mellin transform)

Let $f \in S_x[0, \infty)$. 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.,

$$\forall q > 0 \quad \forall k \in \mathbb{N} \quad \exists C \geq 0 \quad s.t. \quad |\mathcal{M}f(q + it)| \leq C \frac{1}{t^k} \quad \forall t \in \mathbb{R}$$
Measured current is a sigmodial function with short delay, similar to the profiles in some applications (Chen et al., *BioPhysical J.* 76, 1999)

\[
I(t) = \begin{cases} 
0 & t \in (0, t_{\text{Delay}}) \\
I_{\text{Max}} \left[ 1 + \left( \frac{K_I}{t - t_{\text{Delay}}} \right)^{n_I} \right]^{-1} & t > t_{\text{Delay}},
\end{cases}
\]

with \( t_{\text{Delay}} = 30\,\text{ms}, \, n_I \simeq 2.2, \, I_{\text{Max}} = 150\,\text{pA} \) and \( K_I \simeq 100\,\text{ms} \).

**Figure:** \( I(t) \), a sigmodial function

**Figure:** Numerical reconstruction of \( \rho \)

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Merci beaucoup de votre attention !