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To cite this version:

Audrey Houillon, Jacques Droulez. Implementation of a Bayesian Filter in a Photoreceptor Cell. Deuxième conférence française de Neurosciences Computationnelles, "Neurocomp08", Oct 2008, Marseille, France. hal-00331589

HAL Id: hal-00331589

https://hal.science/hal-00331589v1

Submitted on 17 Oct 2008

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IMPLEMENTATION OF A BAYESIAN FILTER IN A PHOTORECEPTOR CELL.

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ABSTRACT
In this study we consider how probability distributions calculated in probabilistic cognitive models can be represented and processed in the brain. More exactly we show that a photoreceptor cell can compute a simple Bayesian inference in a binary Hidden Markov Model (HMM), based on the underlying biochemical interactions of this single cell. We derive, under steady-state conditions, a formal equivalence between the probablistic model and the molecular mechanisms, and show that the equivalence can be extended to the dynamic case. From the photoreceptor example we see that biochemical interactions can represent probability distributions and implement basic probabilistic reasoning.

KEY WORDS
Bayesian Inference, Biochemical Mechanisms, Photoreceptor Cell, Steady-State Approximation.

1 Introduction

Several Bayesian models have been shown to efficiently describe perceptive and behavioural tasks [1, 2, 3, 4, 5, 6, 7]. These models account for the ability to reason with incomplete knowledge about the external world. However it is still unknown how the subjective probability distributions that have to be computed in the models could be represented and processed in the brain. Different levels of analysis can be considered, for instance rate coding in groups of cells [8, 9, 10] or the individual spike event in a single cell [11]. In this work, we will consider the possibility that molecular interactions within a single cell can implement some elementary probabilistic reasoning. The signals processed by such a cell are subject to various uncertainty sources, a process that is reinforced by the stochastic nature of the interactions within the cell. The aim is not to build a complete cognitive model of the world, neither a precise description of biochemical reactions. We rather want to show that a single cell like a photoreceptor yet has the ability to approximate the current state probability distribution of an HMM.

2 Bayesian Filter

Let us consider an agent which has a cognitive description of the world based on a sequence of state variable s^t and an observation variable o^t with a constant time interval Δt between two observations.

The joint probability distribution $P(S^{0:t}O^{0:t})$ can be simplified by the following three assumptions for an HMM [12]:

1. Markov property of order 1, that is the conditional probability distribution of the present state depends only upon the preceding state : $P(S^t|S^{0:t-\Delta t})=P(S^t|S^{t-\Delta t})$
2. The distribution on the present state is independent on anything else before, given the preceding state: $P(S^t|S^{0:t-\Delta t}O^{0:t-\Delta t})=P(S^t|S^{t-\Delta t})$ which is the world-model.
3. The distribution on the present observation is independent on anything else before, given the present state: $P(O^t|S^{0:t}O^{0:t-\Delta t})=P(O^t|S^t)$

and the final decomposition of the joint probability distribution is

$$P(S^{0:T}O^{0:T})=P(S^0)\prod_t^T P(S^t|S^{t-\Delta t})P(O^t|S^t) \qquad (1)$$

From the estimations over s^t given all past and present observations made by the agent, we obtain the prediction, ie. the probability distribution over $s^{t+\Delta t}$ by a marginalization process over the present state s^t

$$P(S^{t+\Delta t}|o^{0:t})=\sum_{S_t} P(S^t|o^{0:t})P(S^{t+\Delta t}|S^t) \qquad (2)$$

This prediction is the prior knowledge for the next time step, ie. the knowledge about the future state of the world given all past and present observations. This "prior knowledge" is then actualised by a bayesian inference with the new observation $o^{t+\Delta t}$ to compute the posterior probability distribution

$$P(S^{t+\Delta t}|o^{0:t+\Delta t})\propto=P(S^{t+\Delta t}|o^{0:t})P(o^{t+\Delta t}|S^{t+\Delta t}) \qquad (3)$$

We will now consider the simple case where the S^t are binary variables. We further suppose that the transition matrix is time invariant, ie. the transition probabilities are independent from the point in time: $P(S^{t+\Delta t}=1|S^t=0)=T_{01}$ and $P(S^{t+\Delta t}=0|S^t=1)=T_{10}$, with the constants T_{01} and T_{10}. For a binary state, the posterior distribution is completely defined by the ratio $u(t)=\frac{P(S^t=1|o^{0:t})}{P(S^t=0|o^{0:t})}$. The updating rule can be reduced to

$$u(t+\Delta t)=f(t+\Delta t)\cdot v(t+\Delta t) \tag{4}$$

with the likelihood ratio $f(t+\Delta t):=\frac{P(o^{t+\Delta t}|S^{t+\Delta t}=1)}{P(o^{t+\Delta t}|S^{t+\Delta t}=0)}$ and the prediction ratio $v(t+\Delta t):=\frac{T_{01}+(1-T_{10})\,u(t)}{1-T_{01}+T_{10}\,u(t)}$.

3 Biochemical Mechanisms

We consider the biochemical reactions underlying phototransduction in a rod photoreceptor cell as shown in Fig.1 . A detailed description of those mechanisms can be found in [13, 14, 15, 16, 17]. Upon absorption of a photon of light by the retinal pigment, the rhodopsin molecule is transformed into an enzymatically activated state that catalyzes the activation of the G protein transducin. Transducin, in turn, activates the phosphodiestarase (PDE) which then catalyses the hydrolysis of the messenger cyclic guanosine monophosphate ($cGMP$) with the activity $\beta(t)$. The consequent reduction of intracellular $[cGMP]$ leads to the closure of $cGMP$-gated ion channels in the plasma membrane, thereby blocking the inward flux of Ca^{2+}. The $Na^{2+}/Ca^{2+},K^+$ exchanger continues to pump out Ca^{2+}, so that the intracellular Ca^{2+} concentration declines during illumination. Calcium regulates the whole molecular process through different feedback mechanisms as for instance guanylate cyclase (GC) activity. The complex $GC{\cdot}GCAP$ ($GCAP$ stands for guanylate cyclase-activating-proteins) catalyzes the production of $cGMP$ out of GTP. But $GC{\cdot}GCAP$ can also bind to Ca^{2+} thereby inducing a conformational change in the macromolecule GC , decreasing its enzymatical activity and therefore the production of $cGMP$. This calcium-dependent feedback speeds up the recovery. Other adaptation mechanisms exist, which will not be pointed out here, as for our purpose we only need to consider a subset of all the reactions involved in phototransduction. In our simplified model the concentrations are considered as homogeneous across the cell compartment and the input evoked by light incidence is the PDE activity $\beta(t)$.

The GC raises the $cGMP$ concentration with activity $\alpha(t)$. Simultaneously the concentration is decreased by the hydrolysis of $cGMP$ to GMP with activity $\beta(t)$, which yields the rate of change:

$$\frac{d[cGMP]}{dt}=\alpha(t)-\beta(t)[cGMP] \tag{5}$$

The binding of $cGMP$ to $cGMP$-gated ion channels opens them, thus controlling indirectly the inflow of Ca^{2+} via ionic channels with a factor η. On the other side the Ca^{2+} concentration is reduced by the $Na^+/Ca^{2+}-K^+$-exchanger by a factor κ:

$$\frac{d[Ca^{2+}]}{dt}=\eta[cGMP]-\kappa[Ca^{2+}] \tag{6}$$

The Ca^{2+} reversibly associates with the membrane macromolecule $GC{\cdot}GCAP$. This macromolecule $GC{\cdot}GCAP$ has a specific receptive site for the ligand Ca^{2+} and the bound form $GC{\cdot}GCAP{\cdot}Ca^{2+}$induces a conformational change in the macromolecule. This interaction can be formally described by a reversible first-order stoichiometric reaction:

$$Ca^{2+}+GC{\cdot}GCAP \underset{k_2}{\overset{k_1}{\longrightarrow}} GC{\cdot}GCAP{\cdot}Ca^{2+} \tag{7}$$

with the on-rate $k_1$and the off-rate k_2. The rate of change of the reaction can be described by the associated differential equation

$$\frac{d[GC{\cdot}GCAP{\cdot}Ca^{2+}]}{dt}=k_1[Ca^{2+}][GC{\cdot}GCAP]-k_2[GC{\cdot}GCAP{\cdot}Ca^{2+}] \tag{8}$$

with the total enzymal concentration $k_3=[GC{\cdot}GCAP]+[GC{\cdot}GCAP{\cdot}Ca^{2+}]$.

$GC{\cdot}GCAP$ and $GC{\cdot}GCAP{\cdot}Ca^{2+}$ are the possible conformational states of the guanylate cyclase: the first state corresponds to a highly active enzymatic activity, while the second (bounded) state corresponds to an enzymatically less active state. This leads to different activities g_1 and g_2 in catalyzing the production of $cGMP$ and the total enzymatical activity of guanylate cyclase can be summarized as:

$$\alpha(t)=g_1[GC{\cdot}GCAP]+g_2[GC{\cdot}GCAP{\cdot}Ca^{2+}] \tag{9}$$

Altogether the equations in $[Ca^{2+}]$, $[cGMP]$ and $[GC{\cdot}GCAP{\cdot}Ca^{2+}]$ form a system of nonlinear coupled differential equations

$$\begin{cases} \frac{d[cGMP]}{dt}=g_1k_3+(g_2-g_1)[GC{\cdot}GCAP{\cdot}Ca^{2+}]-\beta(t)[cGMP] \\ \frac{d[Ca^{2+}]}{dt}=\eta[cGMP]-\kappa[Ca^{2+}] \\ \frac{d[GC{\cdot}GCAP{\cdot}Ca^{2+}]}{dt}=k_1(k_3-[GC{\cdot}GCAP{\cdot}Ca^{2+}])[Ca^{2+}] \\ -k_2[GC{\cdot}GCAP{\cdot}Ca^{2+}] \end{cases} \tag{10}$$

4 Steady-state convergence of both models

The two systems described so far have different intrinsic characteristics. Unlike the biochemical system, the HMM has a discrete time representation and can be defined by two time-varying functions (posterior and likelihood ratios), whereas the biochemical processes are characterised by three time-varying concentrations. The bayesian filter has only two transition probability parameters and two computational

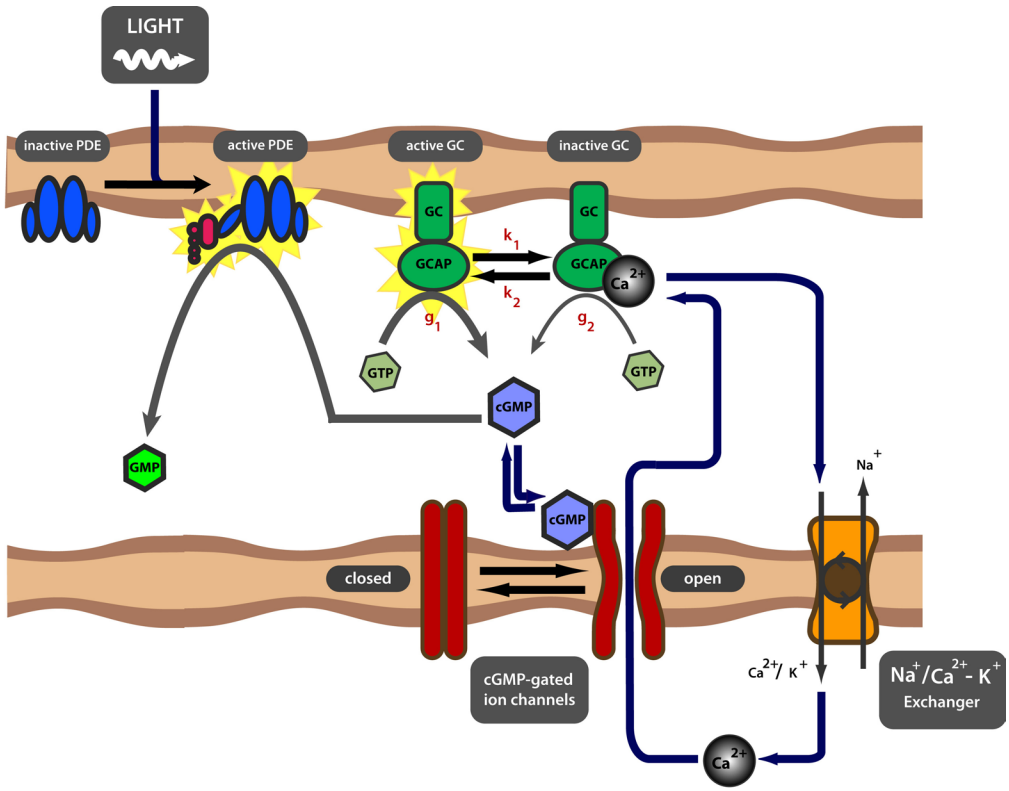

Figure 1. Simplified description of the biochemical mechanisms in a photoreceptor cell: upon absorption of a photon of light $h\nu$ the rhodopsin molecule is enzymatically activated and activates the G protein transducin (not shown) which in turn activates the phosphodiestarase (PDE). PDE catalyses the hydrolysis of $cGMP$. The consequent reduction of intracellular $cGMP$ leads to the closure of $cGMP$-gated ion channels in the plasma membrane, thereby blocking the inward flux of Ca^{2+}. The $Na^{2+}/Ca^{2+},K^{+}$ exchanger continues to pump out Ca^{2+} so that the intracellular Ca^{2+} concentration declines during illumination. Calcium in turn regulates the guanylate cyclase (GC) activity: the complex $GC-GCAP$ catalyzes the production of $cGMP$ out of GTP, but the binding to Ca^{2+} reduces its enzymatical activity and therefore the production of $cGMP$.

steps (prediction and updating) while the photoreceptor mechanisms need seven parameters and three differential equations to be fully described. Nevertheless, the rationale of our approach is to analyse the constraints under which the HMM and the biochemical system converge to the same solution, eg. to a state that can be set equivalent in the sense that $[Ca^{2+}] \propto u(t)$. We derive, under steady-state conditions, a formal equivalence between the bayesian filter and the biochemical mechanisms. Hence, we require the input to both systems to be constant: $\beta(t)=\beta$ in the biochemical system and $f(t)=f$ in the bayesian framework .

At steady-state the updating ratio rule is:

$$u_{ss}^2+u_{ss}\left(\frac{1-T_{01}-f+fT_{10}}{T_{10}}\right)-f\frac{T_{01}}{T_{10}}=0 \tag{11}$$

On the other side, the (chemical) steady-state condition implies that the biochemical variables $[Ca^{2+}]$, $[cGMP]$ and $[GC{\cdot}GCAP{\cdot}Ca^{2+}]$ are constant. Those assumptions also yields a quadratic equation

$$[Ca^{2+}]_{ss}^2+[Ca^{2+}]_{ss}\left(\frac{k_2}{k_1}-\frac{\eta}{\kappa\beta}k_3g_2\right)-\frac{\eta k_3 g_1 k_2}{\kappa\beta k_1}=0 \tag{12}$$

Both variables $[Ca^{2+}]$ and u satisfy a quadratic equation, we consequently make the link between the bayesian filter and the biochemical description by setting the proportionality:

$$[Ca^{2+}]_{ss}=\lambda{\cdot}u_{ss} \tag{13}$$

with the constant λ (μM), and by substituting in eq.(12) and comparing with eq. (11) we get the relations between the parameters of the probabilistic model and the biochemical model

$$\begin{cases} T_{01}=\frac{g_1(\lambda k_1-k_2)}{\lambda k_1(g_1-g_2)} \\ T_{10}=\frac{g_1k_2-\lambda g_2k_1}{k_2(g_1-g_2)} \\ f=\frac{\eta k_3}{\beta\kappa}\frac{(g_1k_2-\lambda g_2k_1)}{\lambda(\lambda k_1-k_2)} \end{cases} \tag{14}$$

Note that several combinations of biochemical parameters lead to the same value of HMM parameters at steady-state, that is the different biochemical systems need not to have the same evolution during transient regimes but will converge to the same stable steady-state solution as the HMM. In fact, the stability of both biochemical and HMM steady-state solutions can be demonstrated.

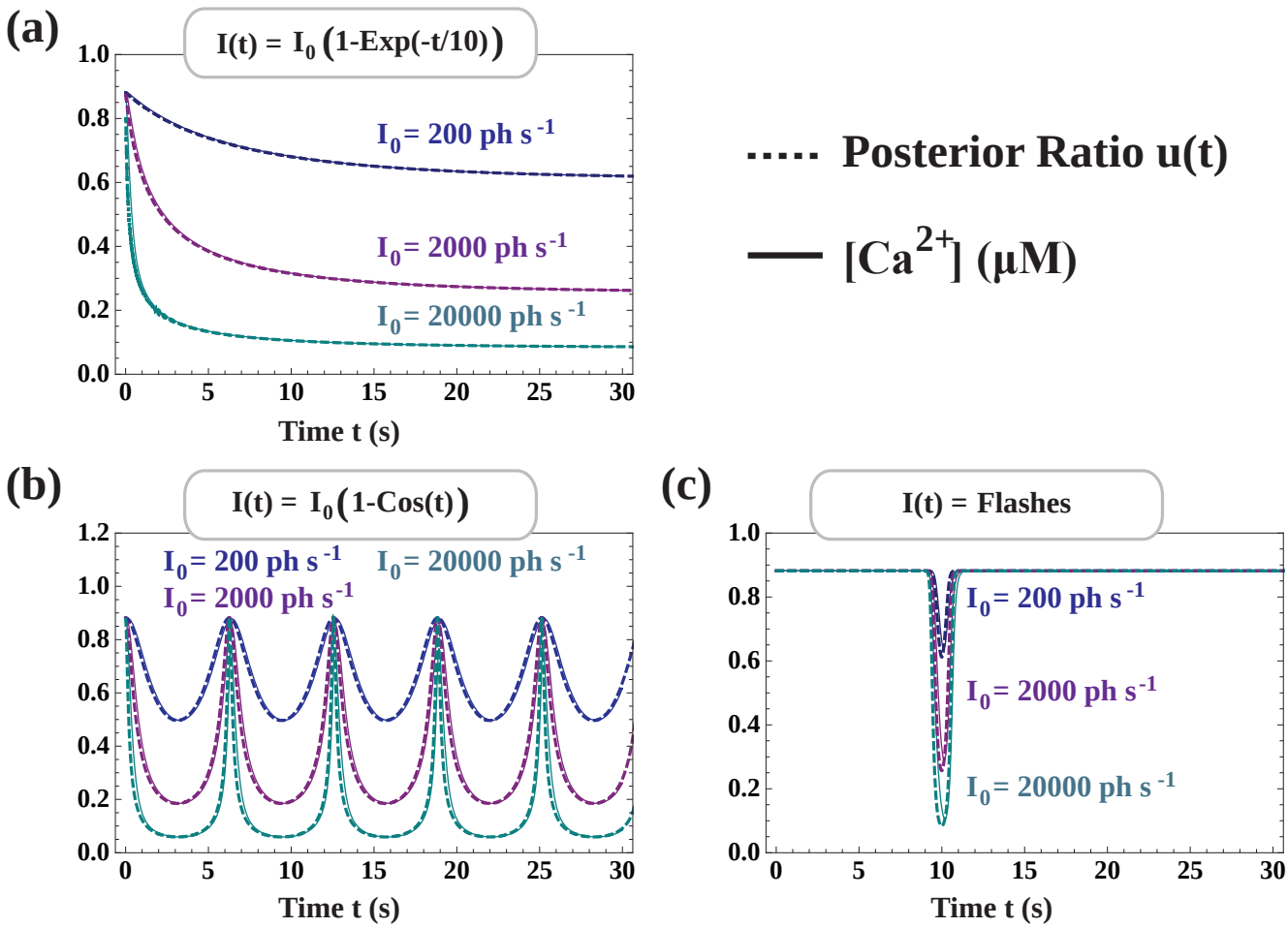

Figure 2. Example of the calcium concentration and the posterior ratio computed for different inputs $\beta(t)$, respectively for three amplitudes I_0. The calcium concentrations are the continuous curve, the posterior ratios are the dashed ones. (a) $I(t)$ tends to a steady value I_0 (b) Periodically varying $I(t)$ (c) Flash input, eg. gaussian function of duration 1 s, for various peak amplitudes I_0. In all cases $[Ca^{2+}]$ and $u(t)$ have almost overlapping temporal evolutions. Parameters used were λ=1 μM, k_1=50·10^3 $\mu M \cdot s^{-1}$, k_2=72 s^{-1}, k_3=30 μM, g_1=70 s^{-1}, g_2=1.7×10^{-3} s^{-1}, η=1 s^{-1}, κ=4 s^{-1}, Δt=10 ms.

5 Results for the dynamical systems

With the parameter equivalence (14) one can conclude that in case of a constant input both systems converge to the same solution (with a proportionality factor λ). We will now consider the case of a varying input and use biologically realistic values for the biochemical parameters. The input is defined as

$$\beta(t)=\beta_{dark}+5.33\times10^{-3}I(t) \tag{15}$$

with $I(t)$ the light intensity arriving on the photoreceptor cell. All parameters were found in literature or derived by fitting the data described in [13]. We simulated the dynamical biochemical system, ie. we calculated the solutions of the general system of differential equations (eq.10) and compared it with the solutions of the bayesian filter, that is we test if

$$[Ca^{2+}]=\lambda\, u(t) \tag{16}$$

We also verified if the dynamical system approximates well the steady-state solutions. The results for three types of time-varying inputs (ie. $\beta(t)$ depends on different light intensity functions (converging input, periodically changing input and flash input, respectively for three distinct peak amplitudes) are shown in Fig. 2 for λ=1 : (a) depicts the response for a steady illumination, the posterior ratio $u(t)$ and the calcium concentration both converge to the same steady state, with a time constant similar to the time constant of the input, ie. the time the illumination needs to reach its steady value. The steady-state values of the posterior ratio $u(t)$ and the calcium concentration are equal. (b) The temporal response for a periodically varing function is also very similar for the posterior ratio and the calcium concentration. (c) For a flash, ie. a gaussian function of 1s duration and three different peak amplitudes. For the parameter space used the temporal evolution are very closed and almost overlapping for a

temporal evolution of the input not being too abrupt, that is the time constant of the input should be approximately of an order 100 greater or more than the sampling step Δt for light intensities ranging from 0 to 100000 photoisiomerizations s^{-1}. Outside this range of values, the transient regimes of both system can differ. The solutions of both systems do not overlap perfectly since the bayesian filter has a slightly faster response than the biochemical system (cannot be observed on the time scale of the graphs shown here).

Thus, the error introduced by the steady-state approximation is negligible for the parameter space described above and the implemention of a bayesian filter by the calcium concentration is still valid for the dynamic case and for time-varying inputs.

6 Discussion

We have shown, from the photoreceptor example, how relatively simple biochemical interactions can represent probability distributions and implement simple probabilistic reasoning. We have not considered the inactivation cascade of phototransduction (which leads to rhodopsin inactivation) and other calcium-dependent adaptation mechanisms, therefore we have no feedback on the input $\beta(t)$. To describe adaptation to the external input some of the biochemical parameters could also be treated as variable. Moreover we have supposed the concentrations to be homogenous across the intracellular space. A more realistic approach would be to consider concentration gradients, diffusion mechanisms and the cell geometry. On the other hand, the bayesian model should be extended to more states and conditional dependencies, or the transition matrix could be time-variant, as an adaptational mechanism .

Aknowledgements

We thank the support of the European Community Project BACS (Bayesian Approach to Cognitive Systems), grant FP6-IST-027140 and Francis Colas for helpful scientific discussions.

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