Biophysical models of sensillum and action potential generator

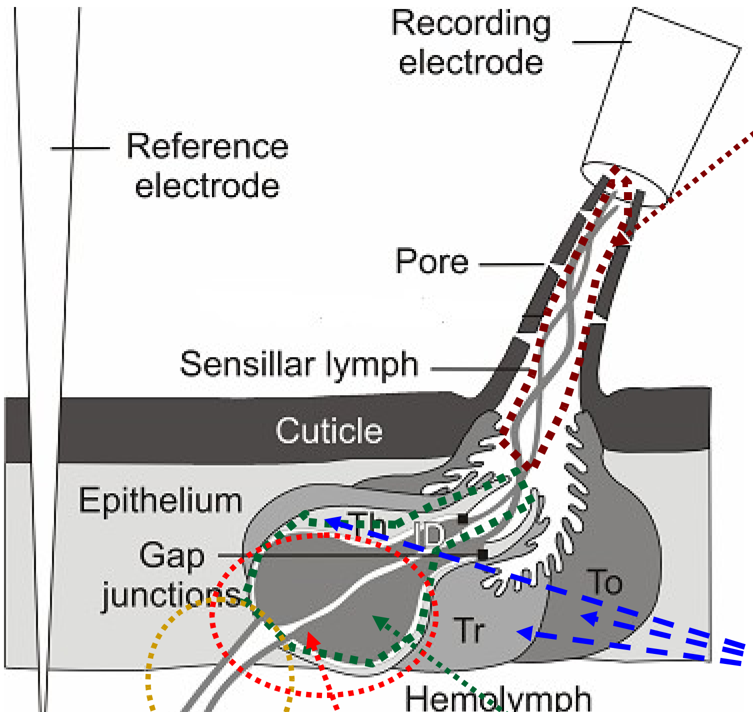
Pherosys meeting 22 June 2009

Yuqiao Gu
INRA , UMR 1272 PISC

Experimental background

- Moth pheromone-sensitive sensillum trichodeum in tip-recording conditions

Record the extracellular potential SP at the tip which is related to the RP



ORN outer dendrite

Pheromone transduction takes place at here and generates receptor potential (RP)

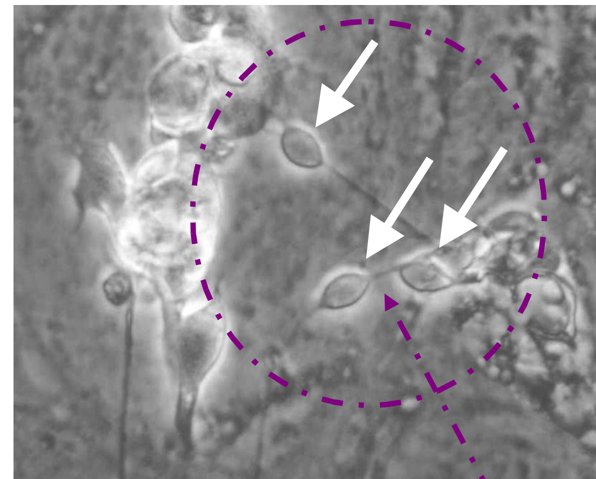
Auxiliary cells

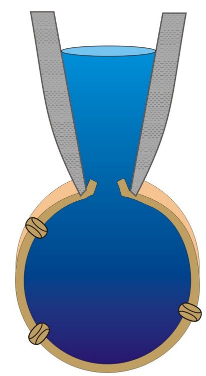
ORN axon

Action potential generation (AP)

ORN soma and inner dendrite

- Primary culture of ORNs and whole-cell patch-clamp





Three ORN cells

Aims

I. Mathematically describe the chemo-electrical transduction taking place at the sensillar lymph and ORN outer dendrite.

II. Using compartmental model to investigate the sensillar circuitry and quantitatively fit to the dose response curves obtained by *tip-recording experiments*.

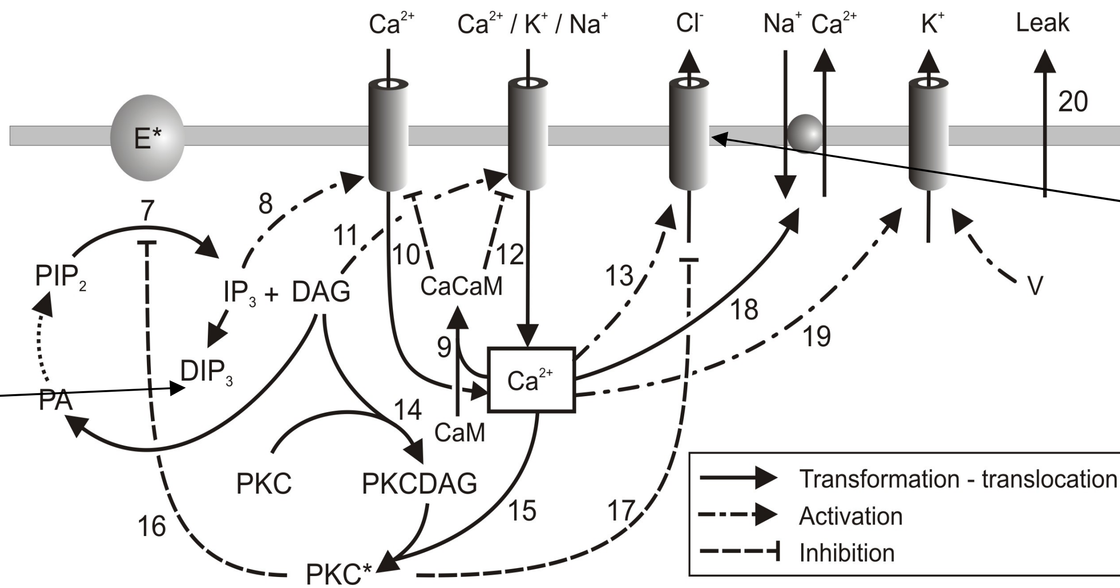
III. Employing Hodgkin-Huxley type model to study the ionic channels generating action potential at the ORN soma and fit to the data obtained by *patch-clamp experiments*.

I

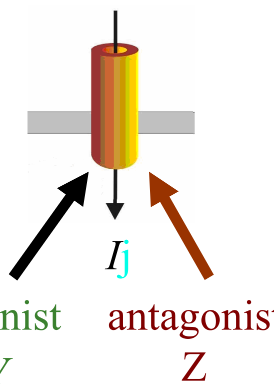
I. Mathematically describe the chemo-electrical transduction taking place at the ORN outer dendrite

➢ The qualitative model

Biochemical reaction Network: steps 7,9, 10, 12,14, 15,16,17



Chemo-electrical transduction network: steps 8,11,13, 18,19,20



➢ The quantitative description of the model

Each reaction is described by mass action law $A + B \underset{k-1}{\overset{k1}{\rightleftarrows}} C$ $\frac{d[C]}{dt} = -\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k_1[A][B] - k_{-1}[C]$

The synthesis rate of the second essenger IP_3 and DAG is described by $v = \frac{s_{M1}}{1+\left(PKC^*(t)/K_{is}\right)^{n_{is}}} \cdot E^*(t)$

Each ionic current, I_j, is given by *Ohm's law* $I_j = G_j(V_{ed} - V_{id} + E_j)$ $G_j = \frac{G_{Mj}}{1+\left(K_j/Y\right)^{n_j}}$

$$K_j = K_{mj}\left(1+\frac{i_{Mj}-1}{1+\left(K_{ij}/Z\right)^{n_{ij}}}\right)$$

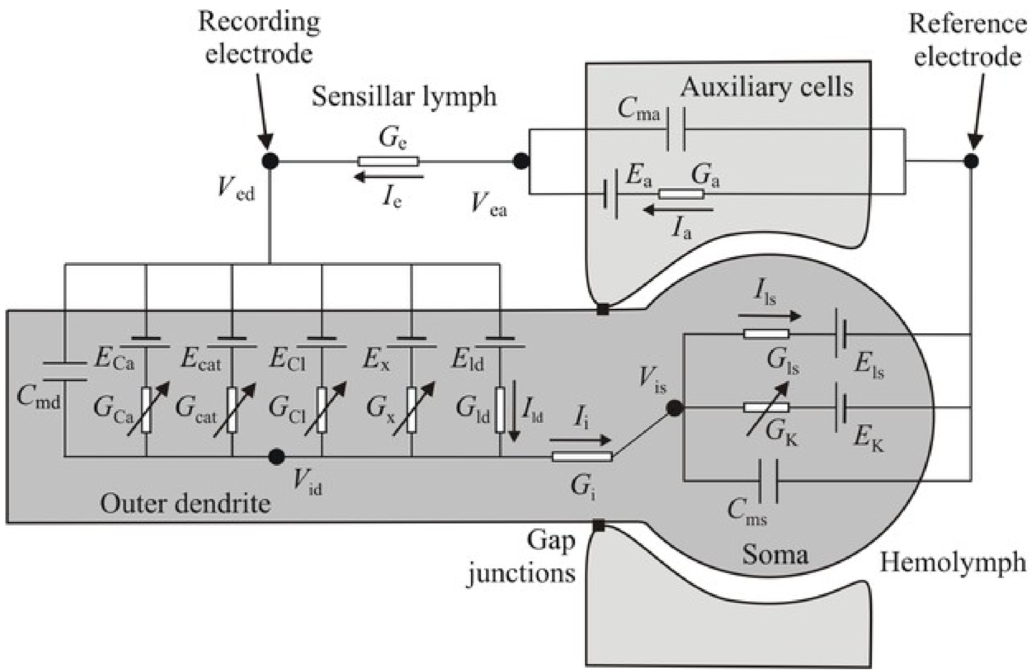
concentration of the antagonist

concentration of the agonist

I

Modeling the electrical network at the sensillum

➢The equivalent circuit of the three-compartment model



➢The quantitative description of the electrical network

The mathematical description of each compartment, k, can be derived from *Kirchhoff's current law*

$$I_{mk} = C_{mk} \frac{dV_k}{dt} + I_{ionk}$$

The receptor potential (RP) at the dendrite is

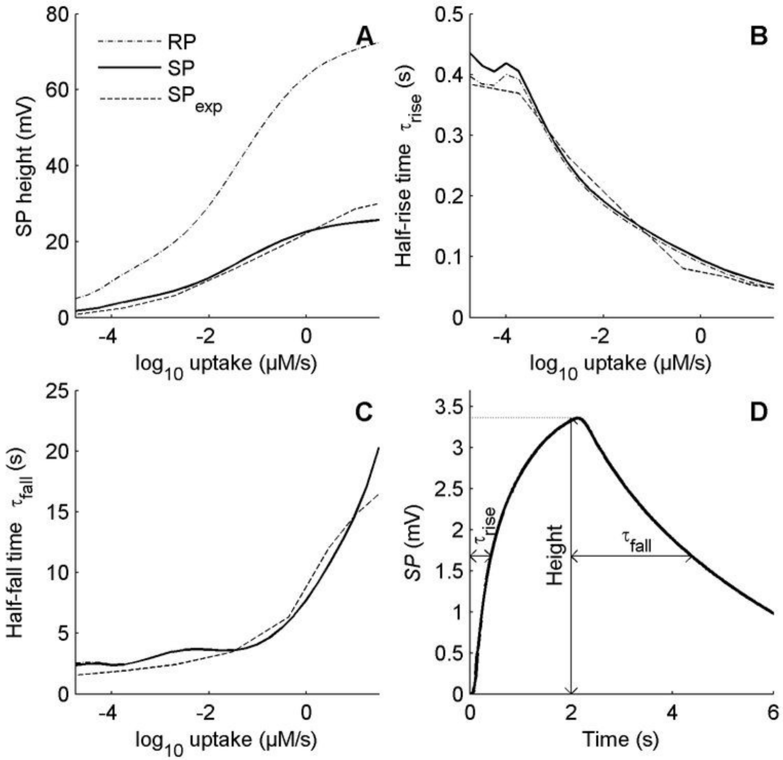
$$RP = (V_{id} - V_{ed}) - (V_{id}0 - V_{ed}0)$$

The measured sensillum potential (SP) by tip-recording experiment is

$$SP = V_{ed} - V_{ed}0$$

I

Fitting to the tip-recorded dose response characteristic function by three-compartment model

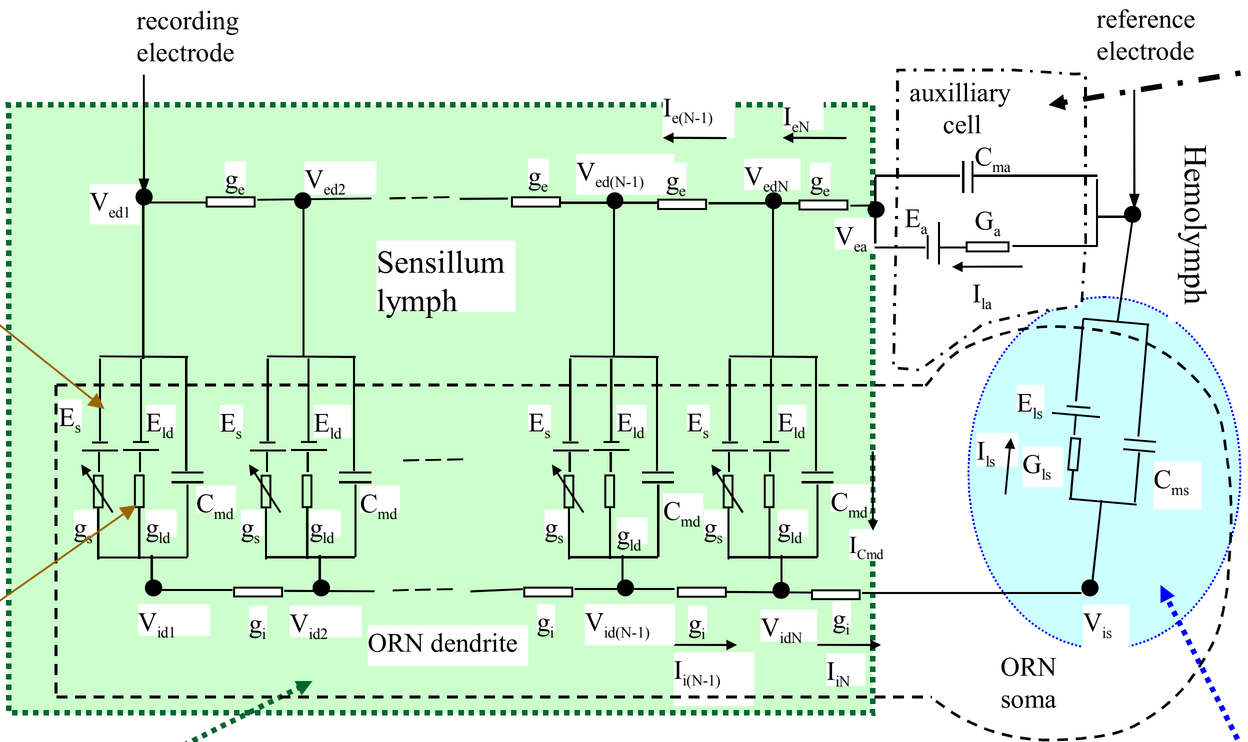


- The heights of *SP* & *RP* are very different, by contrast, their half-rise and half-fall times are closer.

- The model obtained captures the main features of the dose-response curves of SP:
  1) the wide dynamic range from $10^{-4.75}$ μM/s to $10^{1.5}$ μM/s of 6 decades with almost the same saturation amplitudes as the experimental data;
  2) the short rising time;
  3) the long falling time.

II Sensillum model with multicompartmental outer dendrite and its simplification

- The circuit of pure electrical sensillar model with N+2 compartments



One pheromone dependent ion channel with variable conductance

Leak ion channel

N compartments for the outer dendrite and sensillum lymph.

One compartment For the auxiliary Cells.

One compartment for The ORN inner dendrite and soma.

II

➢The quantitative description of the N+2-compartment model

Differential equation for the potential inside the ORN soma

$$\frac{dV_{is}}{dt} = (I_{iN} - I_{Gls})/C_{ms}$$

Differential equation for the potential outside the auxiliary cells

$$\frac{dV_{ea}}{dt} = (I_{la} - I_{eN})/C_{ma}$$

Differential equation for the potential inside the jth compartment of ORN outer dendrite

$$\frac{dV_{idj}}{dt} = \frac{g_e}{C_{md}(g_e + g_i)}(I_{ej-1} - I_{ej} + I_{ldj} + I_{sj}) + \frac{g_e}{C_{ma}(g_e + g_i)}(I_{la} - I_{eN}) + \frac{g_i}{C_{ms}(g_e + g_i)}(I_{iN} - I_{ls})$$

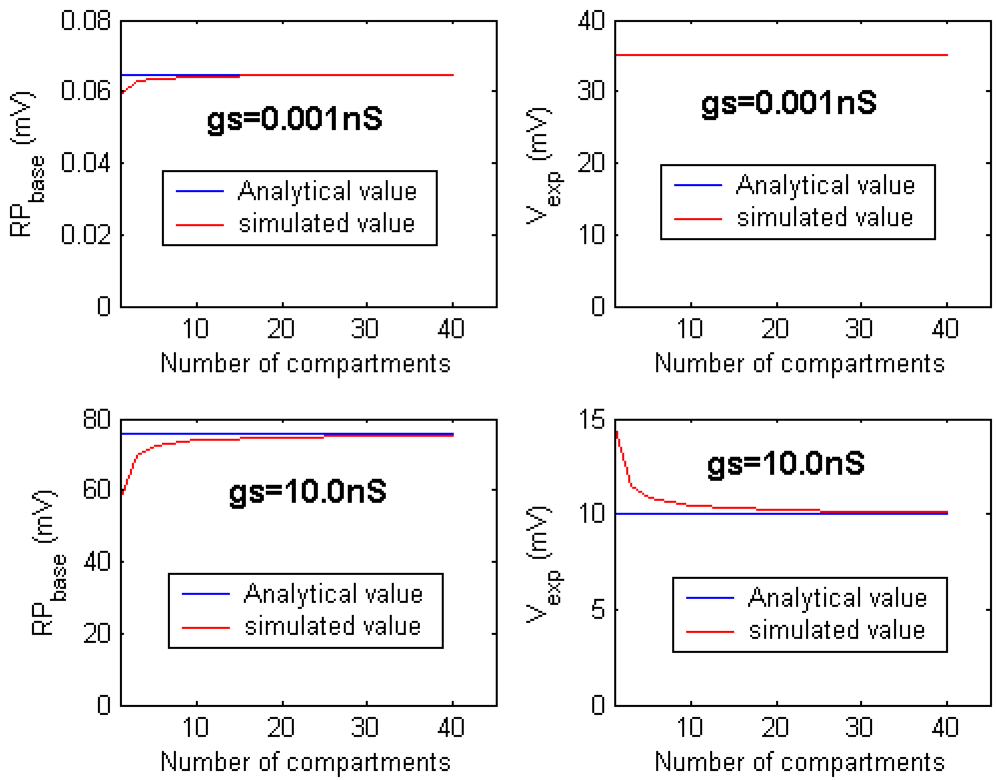
Differential equation for the potential outside the jth compartment of ORN outer dendrite

$$\frac{dV_{edj}}{dt} = \frac{g_i}{C_{md}(g_e + g_i)}(I_{ej} - I_{ej-1} - I_{ldj} - I_{sj}) + \frac{g_e}{C_{ma}(g_e + g_i)}(I_{la} - I_{eN}) + \frac{g_i}{C_{ms}(g_e + g_i)}(I_{iN} - I_{ls})$$

II

Comparing the steady state values of the model with the analysis results

Computer simulations for models with 1 to 40 dendrite compartments were performed and the resulting steady state values were compared with their analytical value obtained by Vermeulen and Rospars in Eur Biophys J (2001) 29:587-596.



The relative error increases with pheromone dependent conductance gs and decreases with number of compartments. It is less than 1% with 40 dendrite compartments and greater than 24% for gs = 10 nS with 1 dendrite compartment.

II Effect of the battery *E*a situated at the auxiliary cells

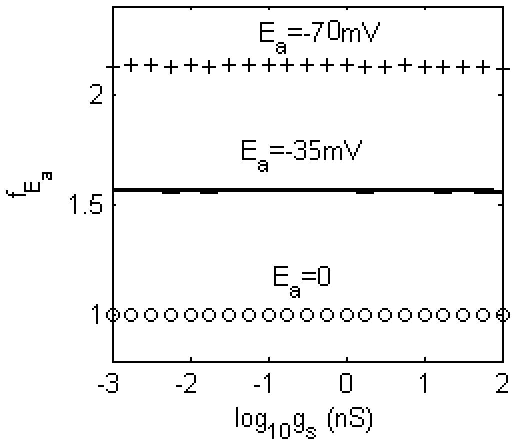
Experimental hypothesis: *E*a plays a functional role in increasing sensitivity.

The height of RP at the dendrite base

Amplification factor of Ea

$$f_{E_a}(\log g_s) = \frac{H_{RP_s}(\log g_s, E_a)}{H_{RP_s}(\log g_s, E_a = 0)}$$

Pheromone dependent conductance

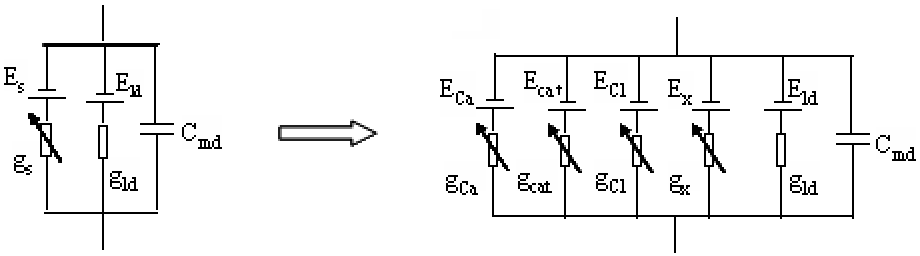


The effect of Ea is linear amplification. The amplification proportion for different stimulation dependent gs is the same.

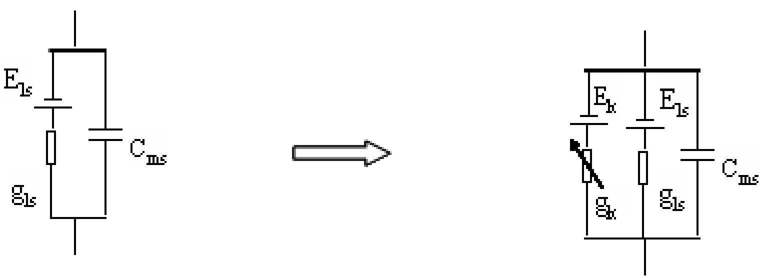
II

Multicompartmental sensillar model with pheromone transduction cascade and realistic channels

The circuit of each compartment
at the ORN outer dendrite

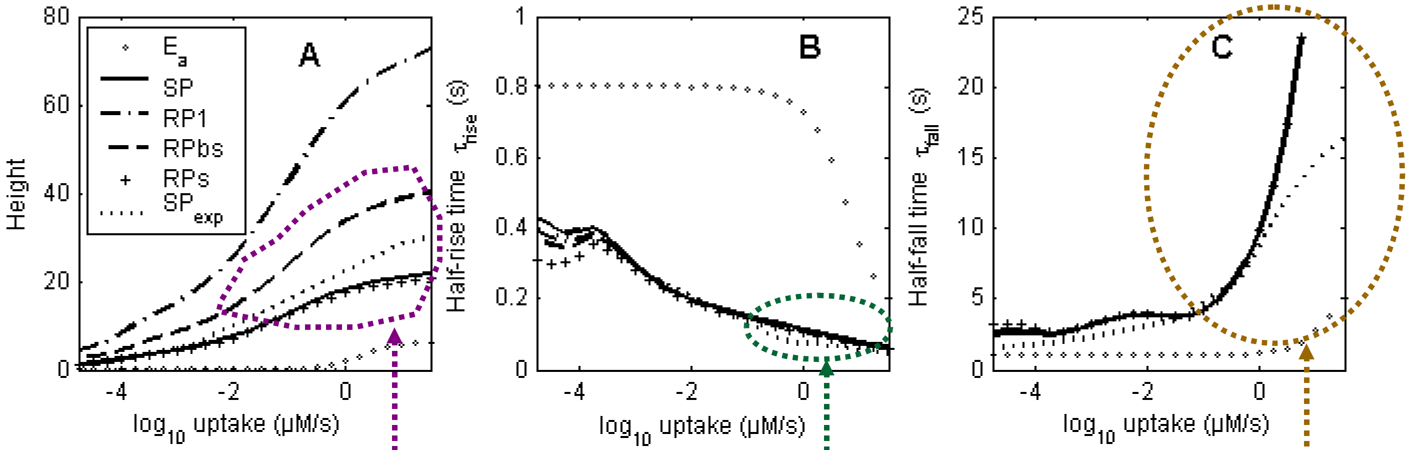


The circuit of
the ORN soma

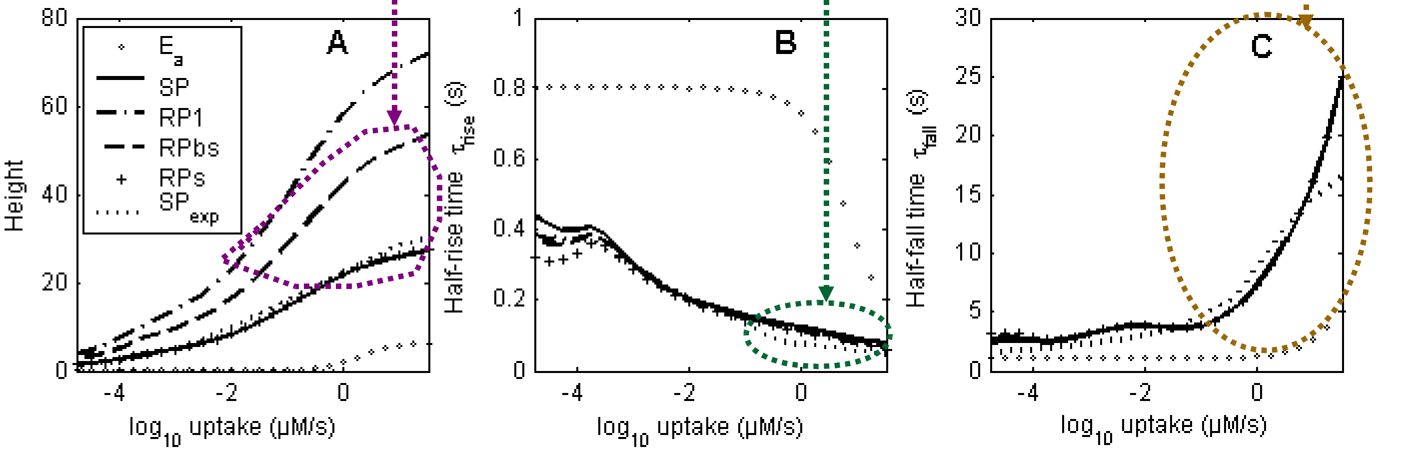


II Comparing simulated dose response curves with those of tip-recorded

Result with one compartment at the outer dendrite

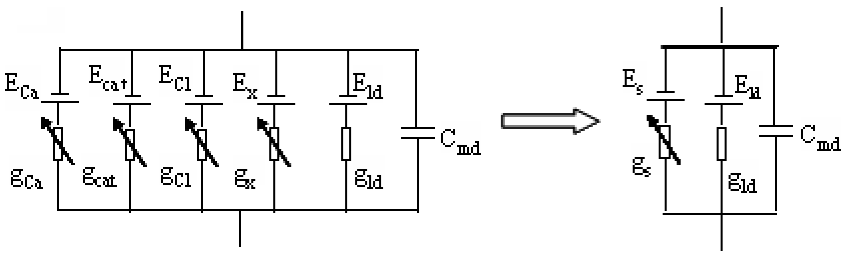


Result with 20 compartments at the outer dendrite



II

Simplification of the multichannel model



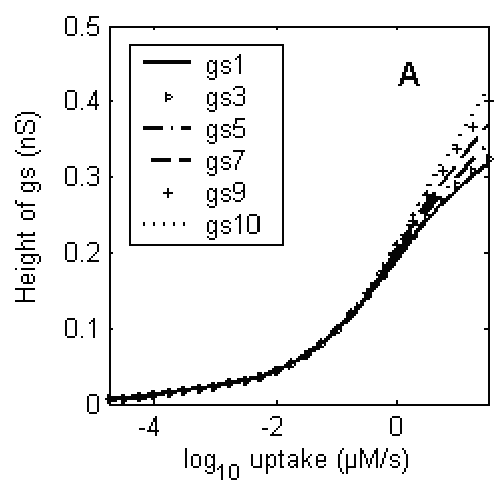
Mathematical conversion:

$$I_{sj} = I_{Caj} + I_{ctj} + I_{Clj} + I_{xj}$$

$$I_{sj} = g_{sj}(V_{edj} - V_{idj} + E_s)$$

$$g_{sj} = (I_{Caj} + I_{ctj} + I_{Clj} + I_{xj})/(V_{edj} - V_{idj} + E_s)$$

For simplicity, let E_s = 0, using this equation, we get g_{sj} for each compartment based on the simulation result on the multiple channels and multiple compartments model.

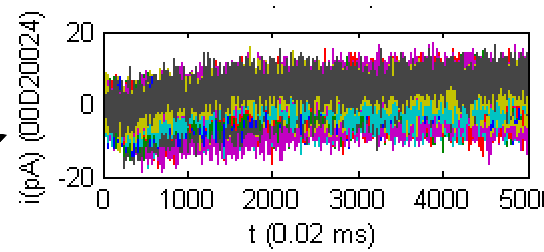


III. Modeling the ion currents through voltage-gated channels generating action potential at the soma and axon initial segment of ORN

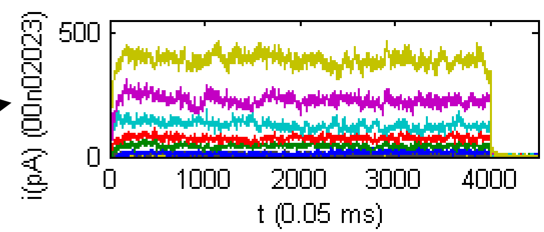
The raw data by Philippe Lucas

Fast sodium current

Transient Ca2+ current

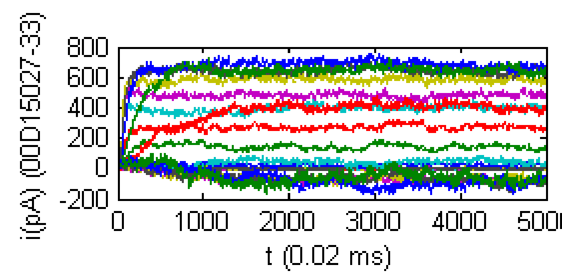


Delayed rectifier potassium current



Transient potassium A current

Calcium-dependent potassium current



III Data preprocessing

Step 1: Removing the artifacts

1) Taking the average of data obtained from 10 to 12 experiments.

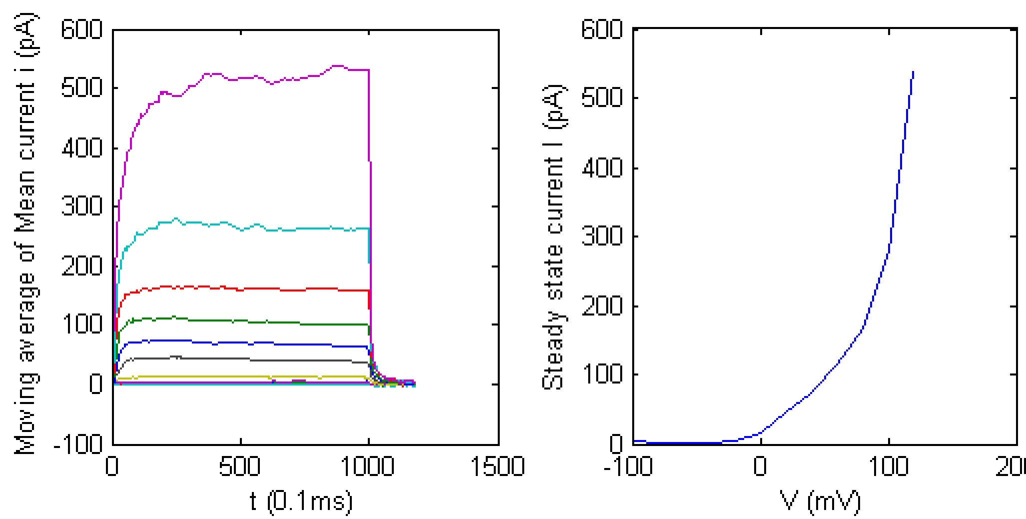
2) Taking the average of the data before and after the artifacts as the value during the artifacts.

Step 2: Removing the noise and smoothing the current curves

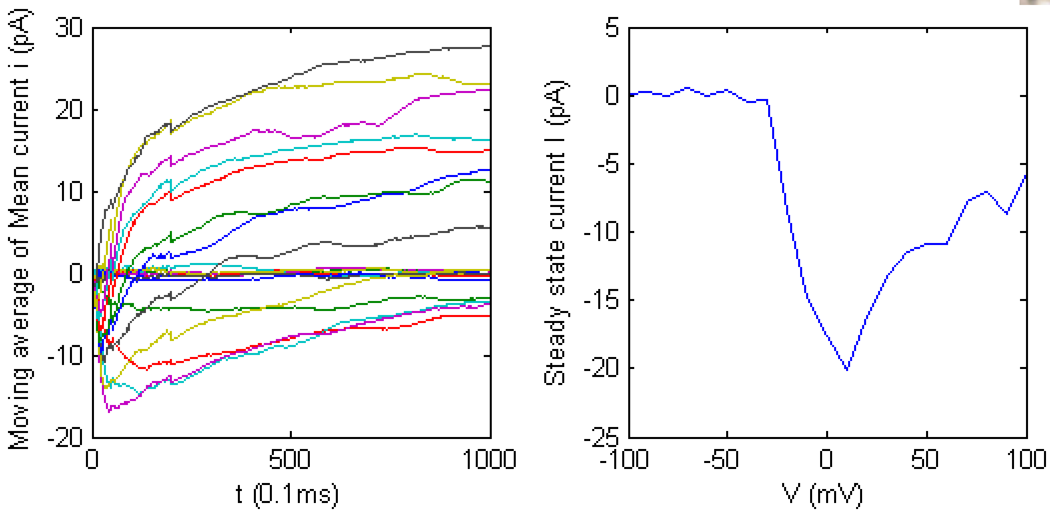
Moving average approach

$$y(i) = \frac{1}{M}\sum_{j=0}^{M-1} x(i+j)$$

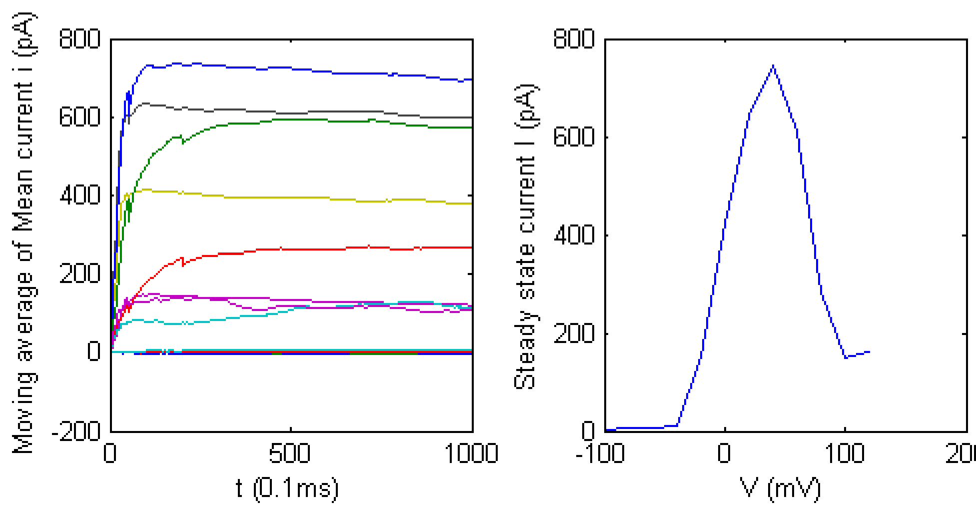
Processed voltage-dependent delayed rectifier K currents



Processed voltage-dependent Ca currents



Processed Ca - and voltage-dependent K currents



III Modeling the ion currents by Hodgkin-Huxley type equations

Maximal conductance

Reversal potential

$$I_{ionaj} = g_j m^M h^N (V_{is} - E_j)$$

Gating variables

$$\dot{m} = (m_\infty (V_{is}) - m) / \tau_m (V_{is}), \qquad 0 \le m(t), h(t) \le 1$$

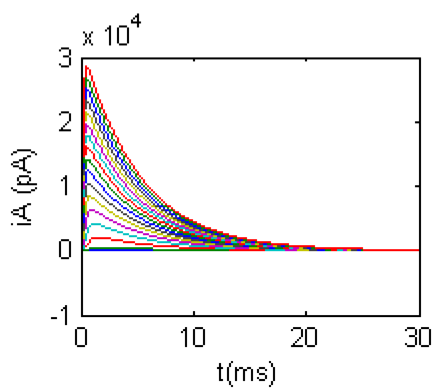
$$\dot{h} = (h_\infty (V_{is}) - h) / \tau_h (V_{is})$$

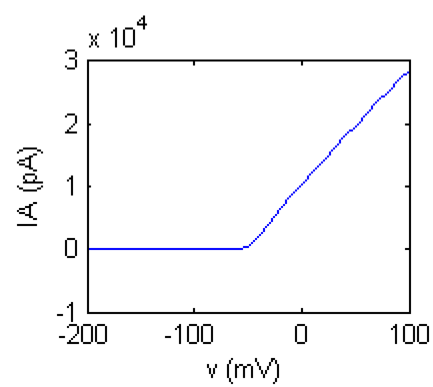
Voltage-dependent steady state value

Voltage-dependent time constants

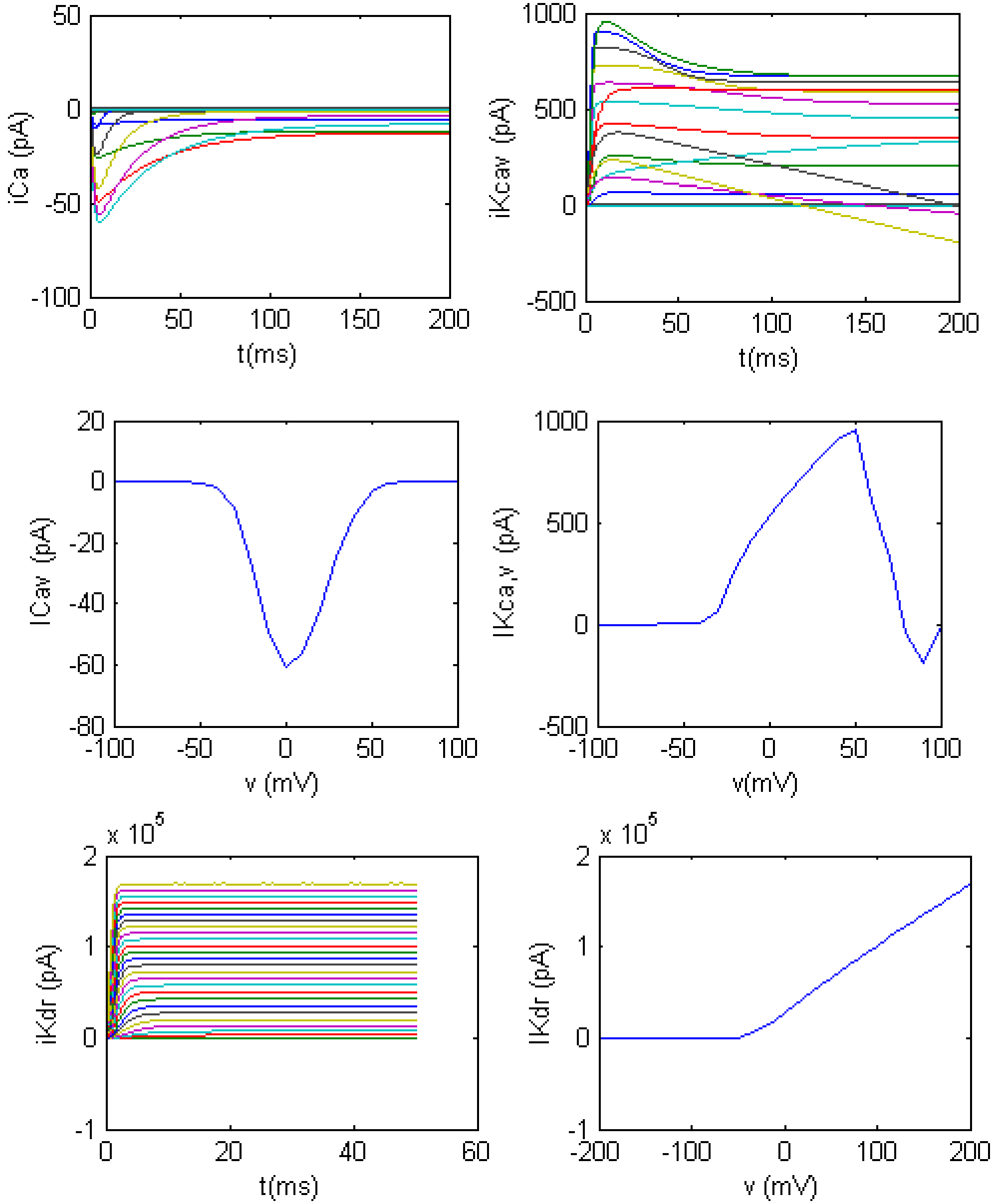
Simulated model results for different type of ion currents

Transient potassium A current





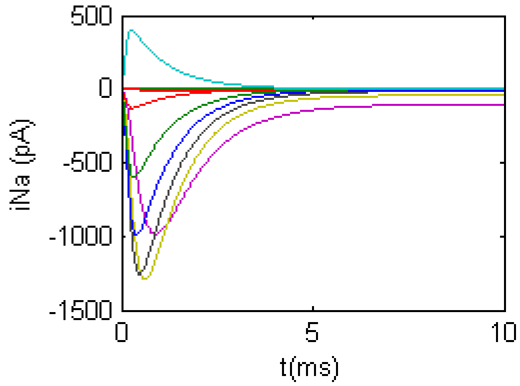
Voltage-gated Ca currents and Ca - and voltage-dependent K currents

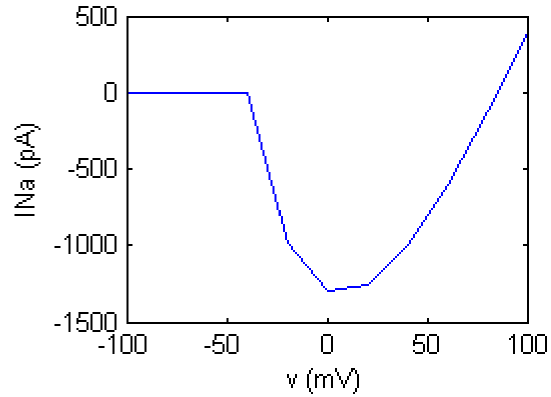


Voltage-gated delayed rectifier K currents

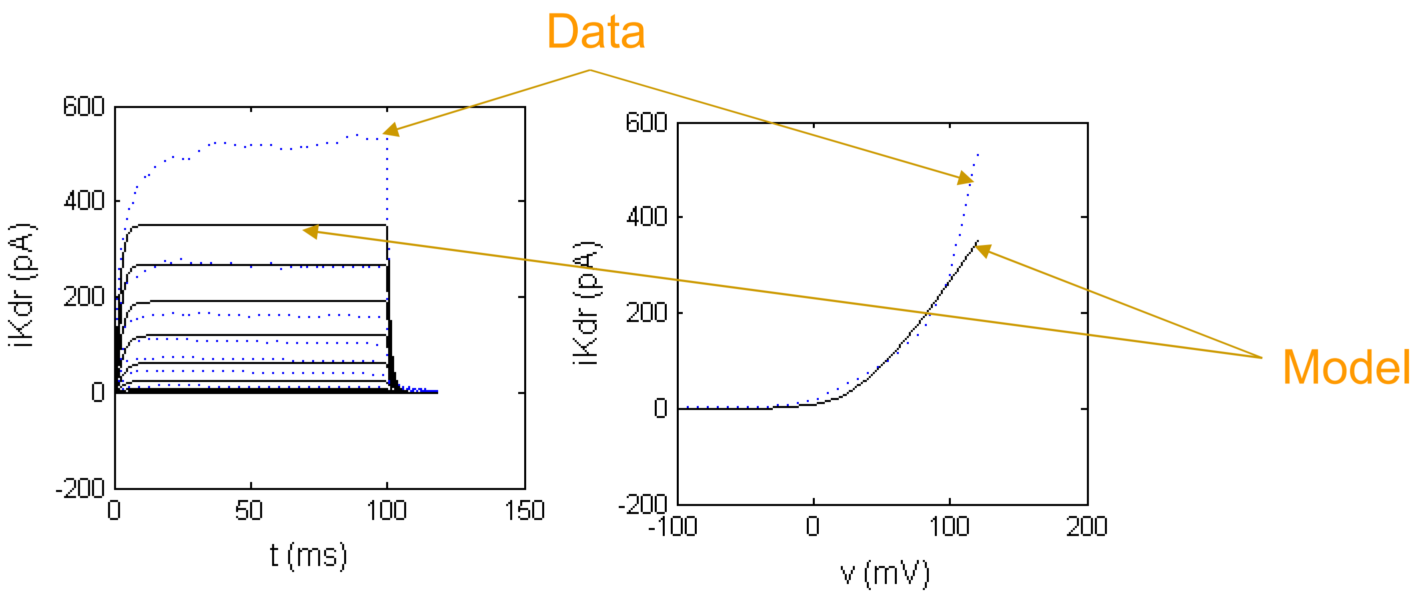
III

Voltage-gated Na currents





Fitting to the data by simulated annealing algorithm



Perspectives

- Properly simplify the detailed sensillar model by including only the major transduction steps and ionic channels: translocation, receptor activation, effector activation,
DAG-
and Ca2+-gated channels.
- Fitting to the experimental data of the voltage-gated and Ca -gated currents at the soma and axon initial segment.

- Built a complete ORN and sensillar model by Including the action potential generators — the voltage- and Ca -gated

Acknowledgement

Prof. Jean-Pierre Rospars

Prof. Philippe Lucas

Prof. Karl-Ernst Kaissling

Thank you for your attention