

# **SimNeuron**

## **Current-and Voltage-Clamp Experiments in Virtual Laboratories**

### **Tutorial**

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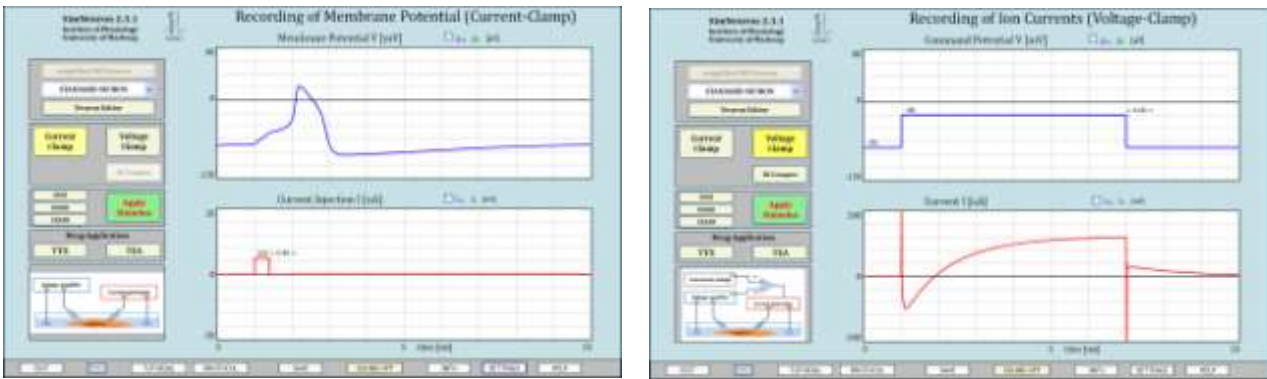
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# 1. Lab Design

We have kept the screen design as simple as possible for easy accessible voltage- and current-clamp experiments, not so much focusing on technical details of experimentation but on a thorough understanding of neuronal excitability in comparison of current-clamp and voltage-clamp recordings.

The **Current-Clamp lab** and **Voltage-Clamp lab** are organized in the same way. On the left hand side, there is a selection box of the already available neurons with several control buttons for your recordings, including a schematic drawing the experimental set-up. The main part of the screen (on the right) is reserved for the diagrams where stimuli can be set and recordings will be displayed.

Initially, you will be in the **Current-Clamp mode** where you will only see a current-pulse (in red) in the lower diagram while the upper diagram should be empty. Entering the **Voltage-Clamp mode** you will find a voltage-pulse in the upper diagram (in blue) with an empty lower diagram. The here displayed recordings (action potential in the current-clamp lab and currents in the voltage clamp lab) will only appear after pressing the “Apply Stimulus” Button.



A band of several **buttons** gives access to additional information, e.g. to open this tutorial directly from the program, or allows changing program pre-“settings” (not possible for demo versions). Especially, you have the possibility to “**SAVE**” your recordings as graphic files on your hard disk

The **Neuron Editor** shows on the left hand side a cartoon of the membrane with the equivalent circuit and the complete set of the **model equations**.

In the mid part, all **parameters values** of the model are shown in text edit boxes and can be modified to examine their effects on the current- and voltage-clamp recordings. The modified neurons can be saved under a new name.

In the **graphics** on the right hand side the impact of some parameter changes on dynamically relevant model features can directly be observed.

## 2. Basic CURRENT-CLAMP Experiments

some basic experiments with only a few mouse-clicks:

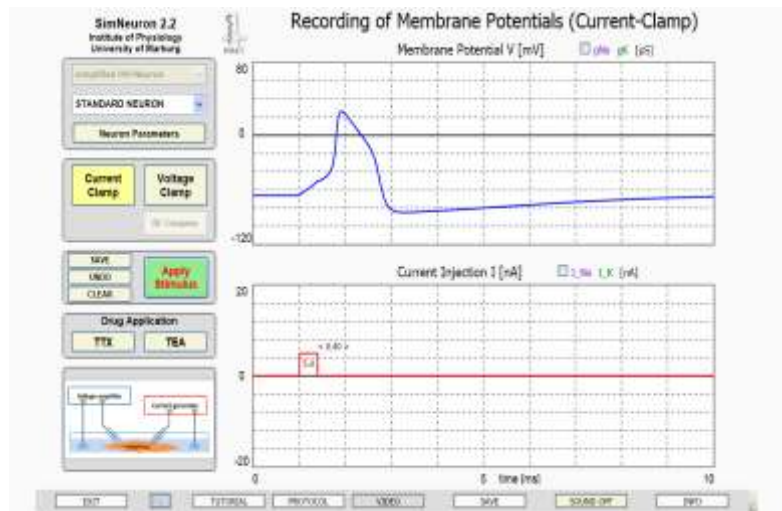
To follow these experiments, please, make sure that you are in the **current-clamp mode** which means that the current-clamp button should be activated (yellow). Initially, “STANDARD NEURON” will be selected and you will find on the right hand side in the lower diagram a **current pulse** (in red).

### 2.1 Action Potential, Conductances and Currents.

Use the initial settings (5 nA, 0.4 ms) and just click on the “Apply Stimulus” button.

An action potential should appear (Fig. 1.1.1, upper diagram in blue).

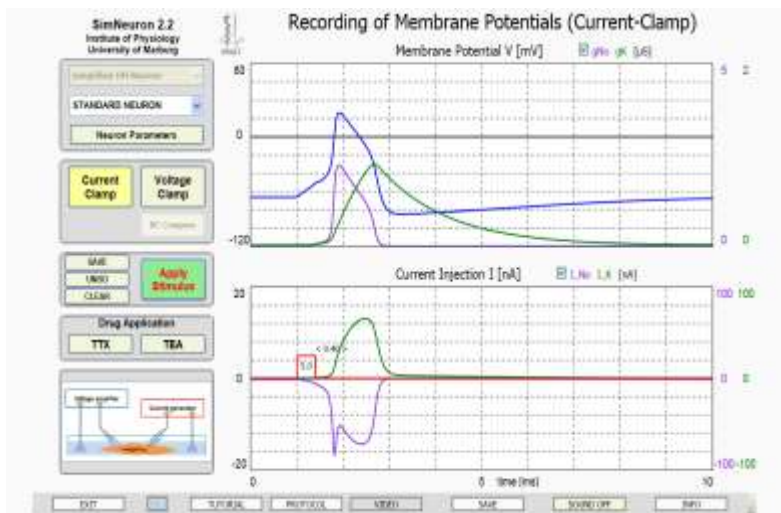
In the virtual lab it is possible what cannot be done in the real experiment, to record simultaneously with the membrane voltage also the time course of ionic conductances and currents. For that, you just have to activate the **check-boxes** for g<sub>Na</sub> g<sub>K</sub> as well as those for I<sub>Na</sub> I<sub>K</sub> above the diagrams.



With next click on “Apply Stimulus” also the ion conductances (in the upper diagram) and the ion currents (in the lower diagram) will be plotted (Fig. 1.1.2), in violet for Na and green for K ions.

In the upper diagram you can see what you know from conventional text-book illustrations, namely that the upstroke of the AP is related to the fast regenerative increase of the Na-conductance (violet) followed by the down stroke, including after-hyperpolarization, due to the delayed opening of K channels (green) combined with the inactivation of Na channels

In the lower part the corresponding changes of the voltage dependent Na and K currents can displayed which you can plot together with their leak currents (incl. I<sub>L</sub>), Additionally can the sum of all currents (SI) cab be displayed



**Question 1.1:** Can you understand the differences in the time course of ionic conductances and currents, e.g. why the Na-current transiently decreases (arrow) or why the K-currents is almost back to zero when the K-conductance is still relatively high?

Hints: use Ohms Law but don't forget to consider the “driving force”.  
Go to the “voltage-clamp experiments” for a better understanding (see below).

## 2.2 Passive Responses and Local Potentials

For the following experiments you should know the meaning of diverse control buttons and learn how to change stimulus-parameters and diagram scaling:

### Change STIMULUS parameters:

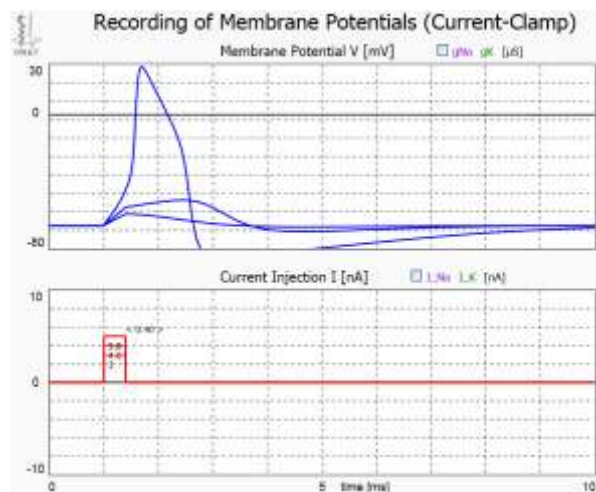
Amplitude and the onset of the pulse can be modified with click on the top or upward deflection of the pulse whereby an up-down or left-right arrow, respectively, will appear. Additionally, the complete pulse can be shifted in time with right mouse click between onset and offset of the pulse.

### Change PLOT parameters (diagram scaling):

Click on one of the numbers in the boxes at the coordinates (voltage, current or time) and select the desired range. Please note: All scaling changes will delete previous recordings.

For the following experiments, chose a voltage range between  $-80$  to  $+30$  mV instead of  $-120 / +80$ ) and, for the current stimulus,  $-10 / +10$  mV instead of  $-20$  to  $+20$  nA. Time resolution is unchanged.

Figure 1.2. shows again the action potential as plotted above - in this case without the ion-conductances and -currents (the corresponding check-boxes are deactivated). Instead, the **SAVE** button has been activated to keep this recording on the screen for comparison with a purely passive response and local potentials.



**Passive Response:** When the active, i.e. voltage-dependent currents are blocked with application of the  $\text{Na}^+$ - and  $\text{K}^+$ -channel blockers “**TTX**” and “**TEA**” (activation of the corresponding buttons) only a so-called passive response remains. The voltage change reflects the charging and discharging of the membrane capacitance by the externally applied current.

### **Supplementary Experiments with TTX and TEA application:**

- Change the strength and duration of the stimulus to see the full charging of the membrane up to the steady state (when a constant potential is reached) and determine the membrane time constant.
- Do the same experiments when only TTX is applied and explain the differences.
- Go back to a short, slightly subthreshold stimulus pulse and compare the action potential with a second one after TEA application. Can you explain why the action potential develops faster and last longer?

**Local Potentials:** Try to adjust the stimulus amplitude to a subthreshold value which nevertheless induces potential changes that are bigger than a pure passive response. These so-called “**local potentials**” develop under contribution of active currents but are still too small to generate an action potential that can be propagated. Physiologically, local potentials mostly appear in form of **synaptic potentials** due to the opening of transmitter gated channels.

## 2.3 The Effects of Stimulus Amplitude and Duration.

When you have tuned the amplitude of the short stimulus of 0.4 ms to a subthreshold value, e.g. from previously 4 nA to 3.5 nA and then increase the stimulus duration, e.g. to 0.6 ms, an action potential again should be elicited due to further depolarization during the additional time which also explains the slight delay.

When you determine the threshold for AP-generation for different combinations of stimulus amplitude and duration you will get the so-called **strength-duration-curve** with the key **rheobase** and **chronaxie**.





**Action Potential Sequences**

With a sufficient long duration of a supra-threshold stimulus a series of action potentials can be generated and you also can see how the stimulus amplitude is encoded in the action potential frequency (firing rate, rate code).

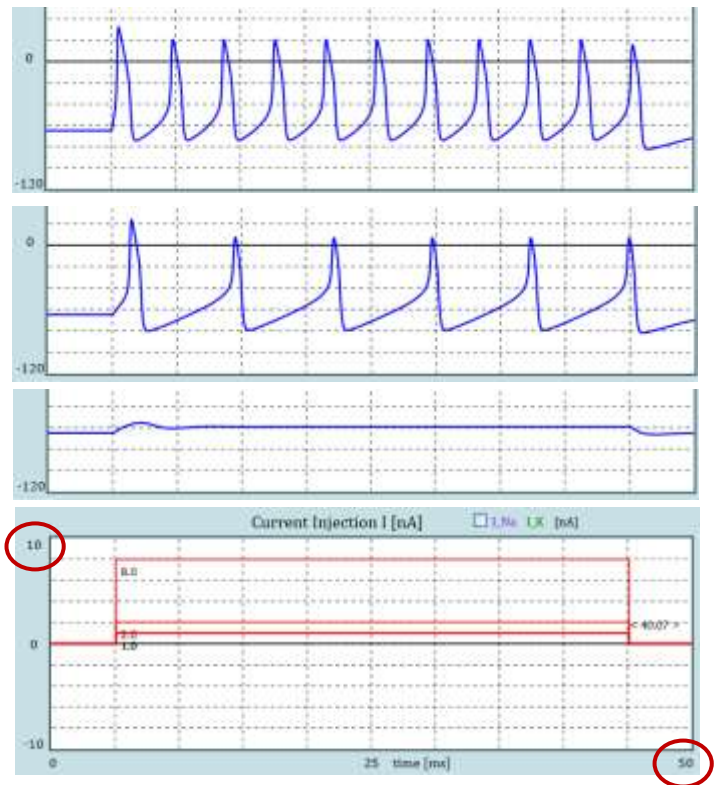
**Scaling:**

*Please note: For these recordings, the time-base has been expanded, here to 50 ms recording time.*

*To adjust the **recording time** click on the maximum value at the abscissa. The same can be done for the adjustments of the **current and voltage range** with click on the maximum values at the ordinates (see circles)*

This figure is composed from three recordings with long lasting stimuli (40 ms) of different amplitudes.

A stimulus strength of 1nA only elicits a slight, local response while the 2nA stimulus generates 6 APs within the given duration and the 8 nA leads to an almost doubled frequency of AP generation..



**Additional experiments:**

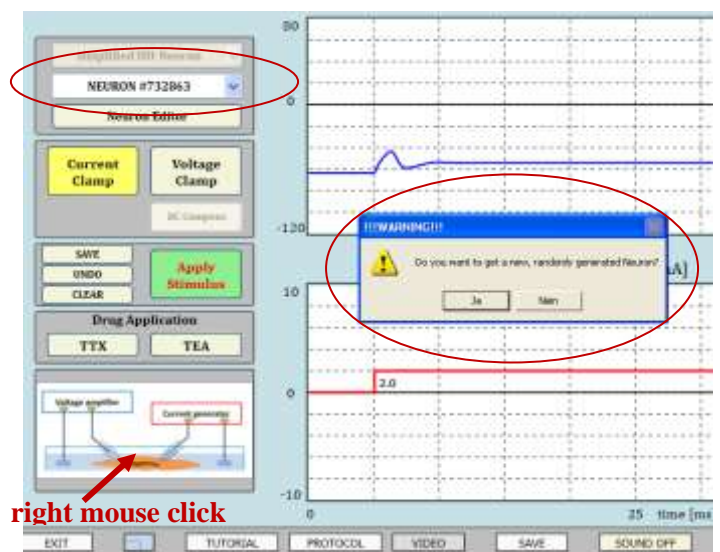
- a) You can systematically increase the stimulus amplitude to determine the frequency – stimulus curve.
- b) Compare the responses of the given “Standard Neuron” with another neuron that you may take from your neuron list, if available, or generate yourself.

**2.4 How to get a New Neuron?**

You can go to the neuron Editor (see below) to modify the neurons parameter values and save the neuron with a new name.

Alternatively, a right mouse click into the schematized recording arrangement (see arrow) will offer a new neuron which will appear in your list of neurons under a randomly generated number (see circles).

Please note: these neurons have random parameter settings. In the given example the new neuron remains subthreshold when the same stimulus is applied which in the Standard neuron elicited a series of APs.



Please note: Depending on the pre-settings, the new neurons may be subjected to “noise”.

### 3. Basic VOLTAGE-CLAMP Experiments

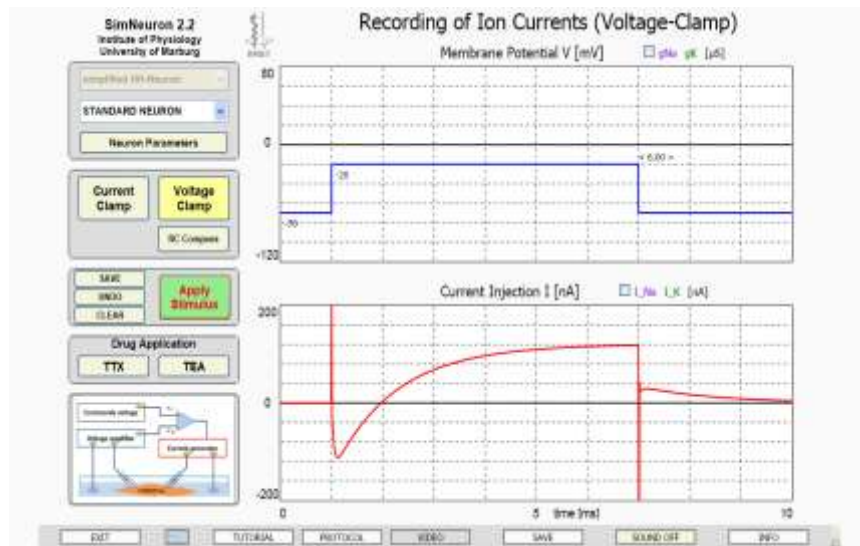
#### 3.1 Capacitive and Voltage-dependent Currents during a Voltage-Clamp Pulse

Go to the voltage clamp lab with click on the “**VOLTAGE CLAMP**” button. Now you will find a voltage pulse in the upper diagram which you can change in the same way as the current pulse in the current-clamp lab.

For the moment, just click on “**APPLY STIMULUS**”.

A typical current curve will appear in the lower diagram:

- 1) There is a brief upward and downward deflection at the beginning and the end of the pulse which reflects the **capacitive currents** that are necessary to charge and recharge the membrane capacitor, i.e. to bring the membrane voltage to the desired values (to the command potential and back to the holding potential).
- 2) In between, there is a downward deflection which turns into an upward deflection (about 1ms after the stimulus onset). These are the currents which are necessary to compensate for the **active, i.e. voltage dependent membrane currents** to keep the potential at the desired value.

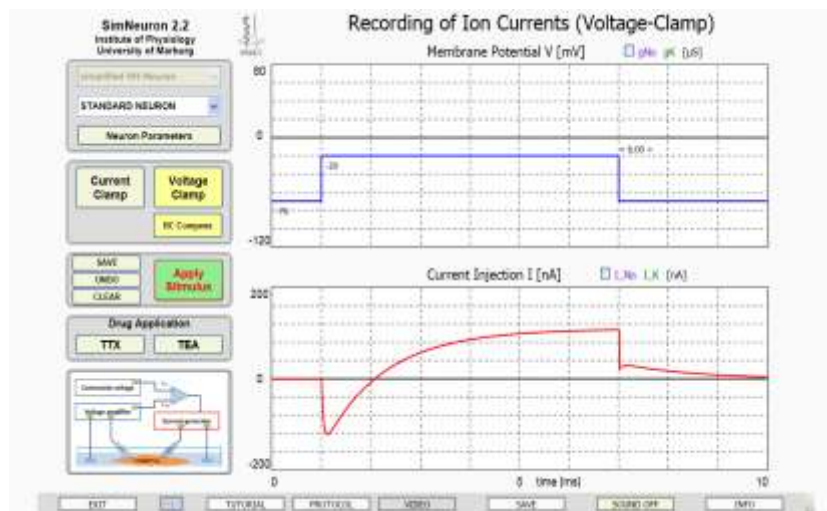


*Please note: a downward deflection reflects an inward membrane current and an upward deflection an outward membrane current.*

#### 3.2 RC-Compensation

The textbooks mostly show recordings where the capacitive currents are eliminated. You can do this here – much easier than in the real experiment – with click on “**RC-compens**” (the only button which does not have a counterpart in the current-clamp lab).

What remains is the transient downward deflection (inward current) that turns into the ongoing upward deflection (outward current).



These are the currents of main interest because these are the “active” currents that develop due to the voltage-dependent opening and closing of ion channels.

### 3.3 Inward and outward currents.

Also in the voltage-clamp lab you can separately plot the  $\text{Na}^+$  (violet) and  $\text{K}^+$  (green) conductances (in the upper diagram) and currents (in the lower diagram) when you activate the corresponding **check-boxes** above the diagrams.

In the lower diagram, you can see that the whole cell current (in red) is the result of a fast transient ( $\text{Na}^+$ ) inward current and a delayed but sustained ( $\text{K}^+$ ) outward current.

### 3.4 Changed command potentials.

Typical voltage-clamp experiments are done with application of a “family” of voltage stimuli with systematically changed command potentials.

With only a few voltage stimuli as shown in the figure it can be demonstrated that the amplitude of the outward current continuously increases while the maximum value of the inward current first increases, then decreases and finally completely disappears

### 3.5 I-V-Curves and “Reversal Potential”

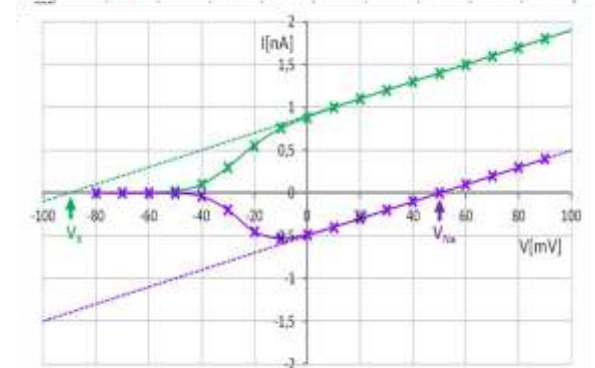
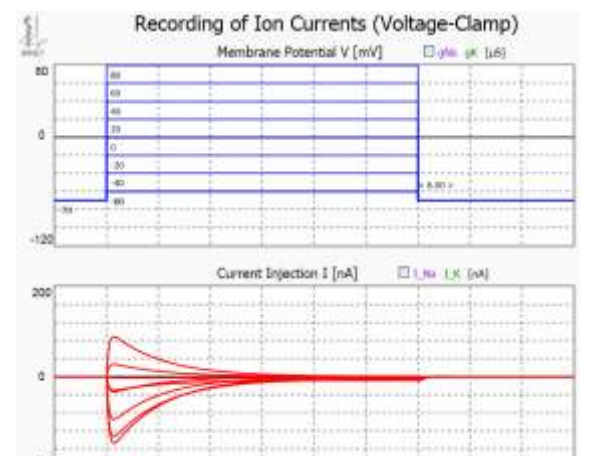
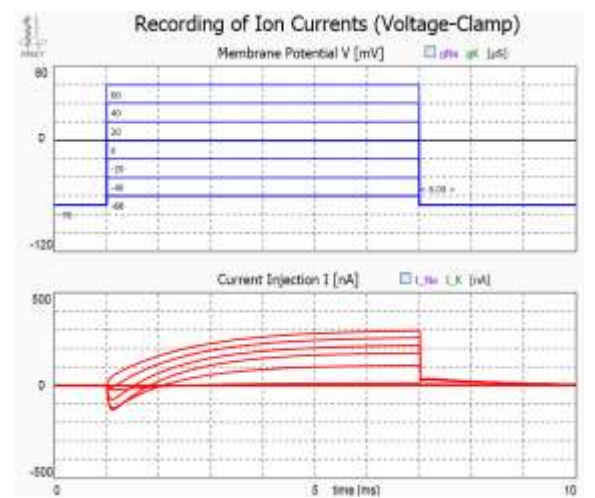
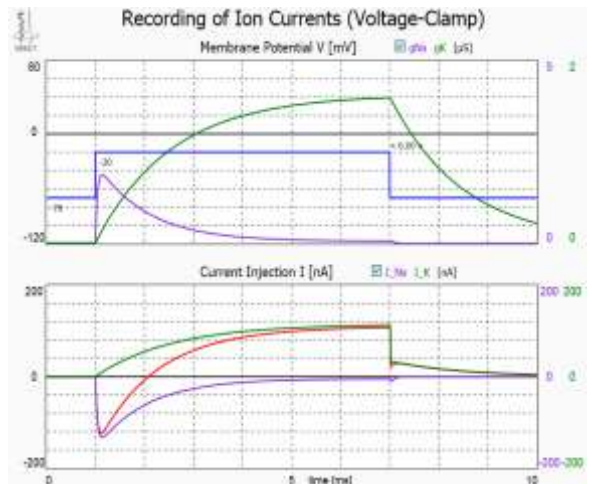
Such experiments are generally done to determine the current-voltage (I-V) curves for specific types of ion channels when other types of channels are blocked. In the given examples, **Na-currents** have been recorded while K-currents were blocked by **TEA**.

Again, you can see that this type of  $\text{Na}^+$  current is inactivating and also that the amplitude of the current is non-monotonically related to the command voltage, even changing its direction from an inward to an outward current.

Back to **Question 1.1** with the observation that the  $\text{Na}^+$ -current transiently decreases during the peak of the action potential (Fig. 1.1.2) Can you now understand why this happens and also why the  $\text{K}^+$ -current is almost zero during the after-hyperpolarization although the  $\text{K}^+$ -conductance is still rather high?

**I-V- curves** are constructed by plotting the maximum currents vs. the command voltage. Examples for both  $\text{Na}^+$  and  $\text{K}^+$  -currents are given in the right lower figure.

At sufficiently high voltages a linear relation appear indicating that the maximum conductance has been reached. The current then only depends on the driving force. Deviations from these linear I-V relations mean that part of the potentially available ion channels are closed. From the relation between the measured current and the current which would be expected when all channels were open, according to the linear curve, the **activation curve** can be constructed.





### 3.6 “Reversal Potentials”

The voltage at which the current changes its direction is called the **reversal potential**. For Na-currents, as shown in the examples above, is this the case at around 50mV. Here, the Na<sup>+</sup>-current is zero although the maximum number of Na-channels should be open. The reason is that, at this point, the “**driving force**” ( $V - V_{Na}$ ) becomes zero. For specific ion channels which are selectively permeable only for one type of ions, this happens at their **equilibrium potentials**, given by the Nernst equation.

*Question: What would be the reversal potential for nonspecific cation channels that let pass monovalent cations like Na and K equally well?*

Reversal potentials are indicative for the type of ion channels and therefore are key values of voltage-clamp recordings. They can be determined by the zero crossing points of the I-V curves which for K-currents requires the elongation of the linear part of the I-V curve.

Moreover, for Na-currents the reversal potential can directly be determined by depolarizing voltage steps in search of the point of zero current in between inward and outward directed currents.

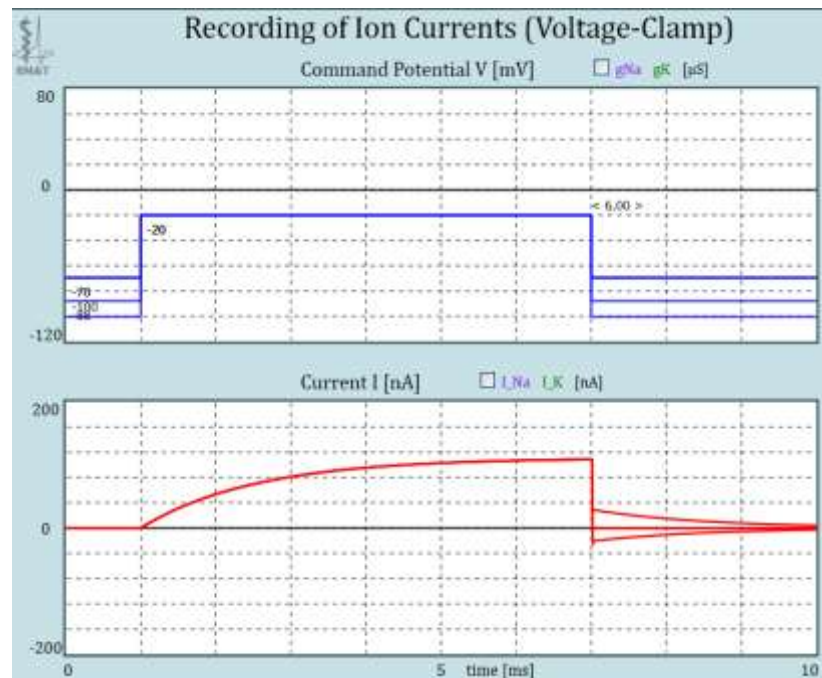
For K currents the reversal potential should be located below the resting membrane potential. With current steps in hyperpolarizing direction, however, these type of K-currents will always be zero, because these type of ion channels will keep closed.

Determining the reversal potential of K-currents, therefore requires a different strategy, namely the recording of “tail currents”.

### 3.7 “Tail Currents”

Tail currents appear at the end of a voltage step due to the delays also of ion channel closing – provided that a driving force unequal zero exists. At the resting membrane potential, this should be the case for both, Na and K currents.

Hence, to determine the reversal potential for K-currents it is necessary to elucidate the voltage where the tail current disappears. For that, instead of changing the command potential you can change the holding potential, as shown in the figure. With blockade of Na currents the tail current becomes zero at the K equilibrium potential.



#### Questions:

- Can you explain why the above shown tail currents would not be significantly different without blockade of the Na currents?
- Why can a reversal potential for non-specific ion channels for Na and K currents be found but not a common reversal potential for both types of ion channels?



### 4. The Neuron Editor

The neuronal responses in the SimNeuron labs are the result of numerical simulations. The “**Neuron-Editor**” provides the possibility to change the values of all model parameters to examine their impact on the neurons’ responses in the current- and voltage-lamp lab.

You can go to the **Neuron Editor** from both labs with click on the corresponding labeled button. Depending on the pre-settings (see below), the access may be password protected.

The screenshot shows the 'Neuron-Editor' interface for a 'STANDARD NEURON'. It includes a list of neurons, a 'to the Lab' button, and several parameter sections:

- Membrane d [μm]:** 56.4, **C<sub>int</sub> [nF]:** 0.100
- Ion Concentrations and Equilibrium Potentials:** [K]<sub>in</sub> 5.0, [K]<sub>out</sub> 150.0, V<sub>K</sub> 90.1, V<sub>Na</sub> 132.0, [Na]<sub>in</sub> 20.0, [Na]<sub>out</sub> 132.0
- Leak Conductances [nS] and Leak voltage [mV]:** g<sub>LK</sub> 180, g<sub>LNa</sub> 30, g<sub>L</sub> 210, V<sub>L</sub> -70.1
- Voltage dependent Ion-Currents:**
  - max. Conductance: g<sub>Na</sub> 4.0, g<sub>K</sub> 2.0
  - half activation potential: V<sub>h</sub> [mV] -22.0, -30.0
  - half inactivation potential: V<sub>1/2</sub> [mV] -50.0
  - slope of activation: z [1/mV] 0.140, 0.140
  - slope of inactivation: s<sub>i</sub> [1/mV] 0.120
  - activation time constant: τ [ms] 0.050, 1.500
  - inactivation time constant: τ<sub>i</sub> [ms] 1.000

On the right, there are three graphs: 'Leak Currents' (I [nA] vs V [mV]), 'Voltage Dependencies' (I vs V [mV]), and 'Time Dependencies' (I vs t [ms]).

**Equations:**

Membrane equation:  
 $-C_{int} \cdot dV/dt = \sum I = I_L + I_{Na} + I_K + I_{act} + I_{inact}$

Leak currents:  
 $I_L = g_L \cdot (V - V_L)$

Voltage and Time dependent currents:  
 $I_{Na} = g_{Na} \cdot m \cdot h \cdot (V - V_{Na})$   
 $I_K = g_K \cdot n \cdot (V - V_K)$

Voltage dependencies:  
 $m_{\infty} = 1 / (1 + \exp\{-z \cdot (V - V_{h,Na})\})$   
 $h_{\infty} = 1 - 1 / (1 + \exp\{-s_i \cdot (V - V_{1/2,Na})\})$   
 $n_{\infty} = 1 / (1 + \exp\{-s_n \cdot (V - V_{h,K})\})$

Time dependencies:  
 $dm/dt = (m_{\infty} - m) / \tau_{Na}$   
 $dh/dt = (h_{\infty} - h) / \tau_{Na}$   
 $dn/dt = (n_{\infty} - n) / \tau_K$

Equilibrium potentials:  
 $V_K = -(R \cdot T / z \cdot F) \cdot \ln([K]_{out} / [K]_{in})$   
 $V_{Na} = -(R \cdot T / z \cdot F) \cdot \ln([Na]_{out} / [Na]_{in})$

Noise current:  
 $I_{act} = \cos(2\pi \cdot b \cdot t) \cdot \sqrt{4 \cdot g_{act} \cdot (dV/dt) \cdot I_{act}}$

In the left upper corner you will find the **list of neurons** that already have been generated and saved. At the beginning, you will only find the Standard Neuron. You can select one of the available neurons to change its parameter values and then can go “**to the lab**” to check its responses. As long as the modified neuron is not yet saved its name will appear with the extension \*test\*. You can “**Save**” your new neuron under the same name (prohibited for the “Standard Neuron”) or under a different name. Likewise, selected neurons can be “**Deleted**”. “**Cancel**” will bring you back to the lab without considering any changes since the last entering of the Neuron Editor.

Below these edit boxes, there is a simple sketch of the **membrane** with ions and ion channels together with the corresponding electric **equivalent circuit**. Below, the complete set of **Equations** is given. The mid-part shows the **numerical values** of all **membrane parameters**, adjustable by **text-edit boxes**. The **diagrams** on the right are for graphical illustrations of some functionally relevant characteristics.

The most upper text edit boxes indicate the **diameter** and membrane **capacitance** of the selected neuron.

The following text-edit boxes (“**Membrane Settings**” with “**Ion Concentrations and Equilibrium Potentials**”, “**Leak Conductances and Leak Voltages**”) are related to the so-called passive membrane properties. which, in computer modeling studies, are mostly represented by a single term for a leak current  $I_L = g_L \cdot (V - V_L)$ , thus only depending on a generalized leak conductance  $g_L$  and the driving force  $(V - V_L)$ . “SimNeuron” allows to separately adjusting the major **leak conductances** and also their **equilibrium (Nernst) potentials**, the latter indirectly with alterations of the **ion concentrations** as the physiologically relevant parameters. The effects of such parameter changes can directly be observed in upper right diagram labeled “Leak Currents”.

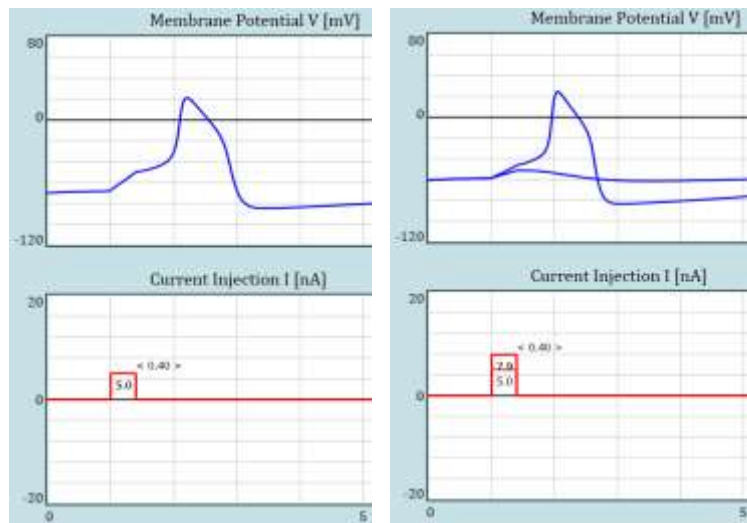
In the lower part, the numerical parameters of the “**Voltage-Dependent Ion-Currents**” are given according to the equations on the left. The thereby induced alterations of the voltage and time-dependencies of the variables  $m$ ,  $n$ , and  $h$  can be observed in the corresponding graphs on the right

Two additional check boxes allow to add and to adjust a “**noise**” current in adjustable intensity  $D$  or to display in addition to the control potential  $V_C$  also the real membrane potential  $V_M$  (in voltage-clamp mode).

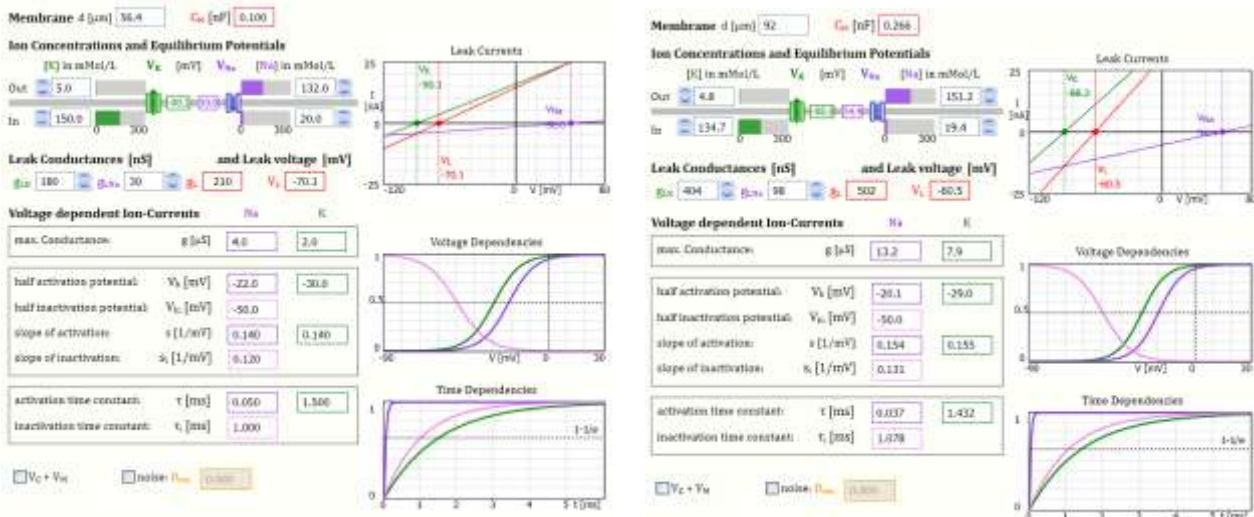
### 4.1 Comparison of Membrane Parameters

It has been taken care that all neurons for experimentation in the SimNeuron laboratories will initially be in a steady, i.e. exhibiting a stable membrane potential. Indeed, new generated neurons will have random parameter settings, however within an accordingly adjusted range. The reason is that you should have the possibility, as one of the first tasks, to determine the threshold of action potential (AP) generation. Indeed, you will see that the required current strength can be significantly different.

The examples compare the Standard Neuron (SN) with a neuron of random parameter settings. Current injection of 5nA which induces an AP in the SN leads in the second neuron to an only slight depolarization. Here, an almost 8 nA stimulus pulse of the same duration is required to generate an AP, although it is in a more depolarized resting state.



Finding out the possible reason for the higher threshold you can go to the Neuron Editor to compare the parameter values. .



Indeed, the **leak potential  $V_L$**  is on an almost 10mV more depolarized level (-60.5mV vs. -70.1mV). However, also the **leak conductance  $g_L$** , stabilizing the membrane potential, is much higher (almost by the factor 2.5) what also can be recognized in the steeper I-V lines of the Leak Currents. Especially, the **diameter  $d$**  of the neuron is almost twice as big which leads to a membrane **capacitance  $C$**  that is by a factor 2.66 bigger than that of the standard neuron. Charging a bigger capacitance needs more current.

Also the parameters of the voltage dependent currents are significantly different. The **maximum conductances  $g$**  for both  $Na^+$ - and  $K^+$ -ions are around 4 times bigger. These, however, are mainly of

relevance for the size of the action potential in relation to the membrane capacitance to be charged and discharged within a given time. The **time constants** are apparently not significantly different. Also the **voltage dependencies** seem to be quite similar, therefore not so much contributing to the increased threshold of AP generation. Likewise, differences in the **ion concentrations**, determining the **equilibrium potentials**, may not play a significant role.

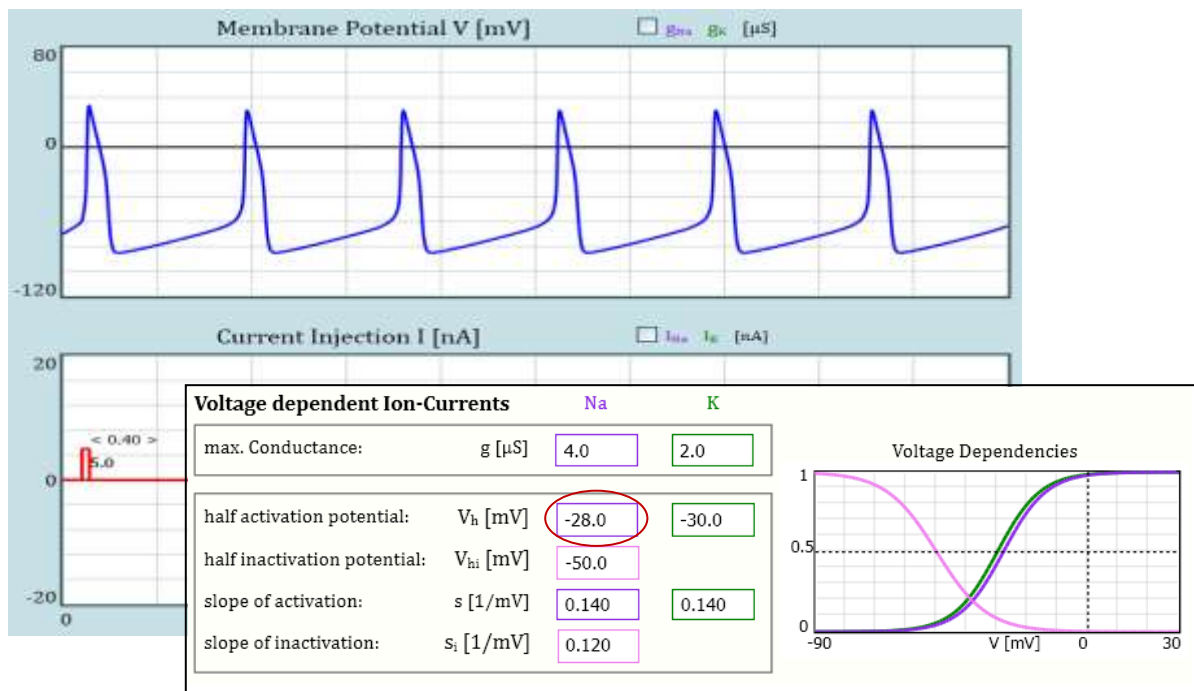
Hence, in this example it seems mainly to be the so-called passive membrane properties (**capacitance and leak conductance**) that are responsible for the increased threshold of spike generation. In other examples it could likewise be voltage dependent currents or the ion concentrations. This can be examined with selective alterations of specific membrane parameters.

## 4.2 Alteration of Membrane Parameters

We are using the Standard Neuron with its defined parameter settings to illustrate the potential impact of some specific membrane parameters on the neurons' excitability.

### 4.2.1 Shift of voltage dependent activation of Na<sup>+</sup> currents – creating a pacemaker neuron

The relation between the activation range of Na<sup>+</sup> and K<sup>+</sup> currents and especially their relation to the leak potential are exceptionally sensitive parameters in determining the neurons' excitability. For example, shifting the half activation potential V<sub>h</sub> for Na<sup>+</sup> channels slightly to more negative potentials (from 22mV to 28mV, see red circle in the figure inset) has dramatic effects. This turns the Standard Neuron with a stable membrane potential into a pacemaker cell which is repeatedly generating APs, even without any external stimulus. The stimulus pulse at the beginning, overlapping with a spontaneously generated AP, does not play a role. For better illustration of the repetitive activity, the recording time in the figure below has been expanded to 50ms.



### 4.2.2 Increasing the external K<sup>+</sup> concentration - via pacemaker activity into a depolarization block #####

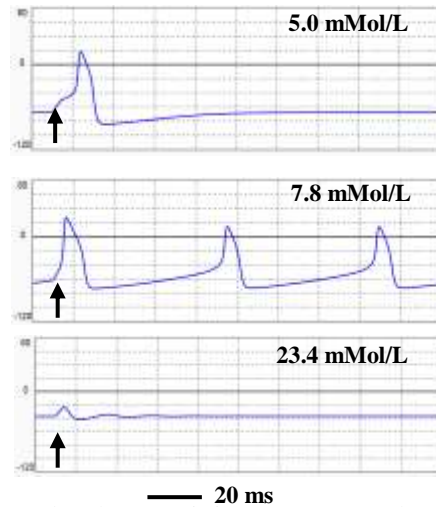
Similar effects, changing a silent neuron into a pacemaker, can be achieved in several different ways. One more example is given below by increasing the external K<sup>+</sup>-concentration. The first, direct effect is a reduction of the K<sup>+</sup> equilibrium potential. This is accompanied by a likewise reduced leak potential. The dynamically relevant effect is the same as before: The Na<sup>+</sup> activation curve and the leak potential are



coming closer together. Spontaneous activity appears when sufficient  $\text{Na}^+$  current is activated for regenerative depolarization already at the level of the leak potential.

Changing external ion concentration is widely used practice in experimental research. Increasing the extracellular  $\text{K}^+$  concentration is common practice even in clinical situations, e.g. bringing the heart into a depolarization block for surgery. The same happens in neurons with sufficient high  $\text{K}^+$  concentrations leading to sufficient depolarization. When the membrane cannot repolarize, the  $\text{Na}^+$  channels will keep in the inactivated state.

The examples on the right show, in the upper trace, the original situation with 5.0 mMol/L external  $\text{K}^+$  concentration where the neuron is in the steady state but can be excited by an external current stimulus (arrow). With 7.8 mMol/L the neuron is sufficiently depolarized for spontaneous AP generation. With 23.4 mMol/L, still much less than the intracellular  $\text{K}^+$  concentration of 150 mMol/L, the neuron keeps depolarized at approximately -40 mV where most  $\text{Na}^+$  channels already are inactivated. The remaining ones can only induce a tiny AP that will completely diminish with further depolarization by further increased  $\text{K}^+$  concentration

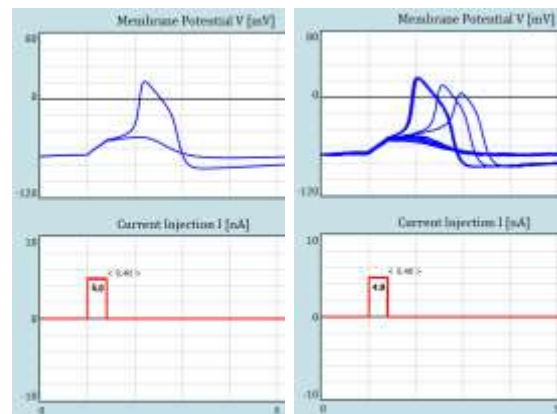


### 4.3 Introducing Randomness: Noise Current

All experimental recordings are contaminated by certain randomness. Apart from the diversity of the neurons, also the same neuron will never react in exactly the same way even on completely identical stimuli. Indeed, there will be not much difference when very strong supra-threshold stimuli are applied. However, in the neighborhood of the threshold of AP generation, tiny random fluctuations may be sufficient to decide whether an AP is generated or not. In reality, such randomness may be of different origin. Here, as in most modeling studies, it is introduced by a noise current accounting for random fluctuations over time.

The initially set stimulus values (5 nA, 4 ms) seem to be just above the AP generating threshold for the Standard Neuron. On repeated application of this stimulus you will always find exactly the same time-course of the action potential. With a slight reduction of the stimulus strength to 4.8 nA an action potential will never appear (see examples on the left).

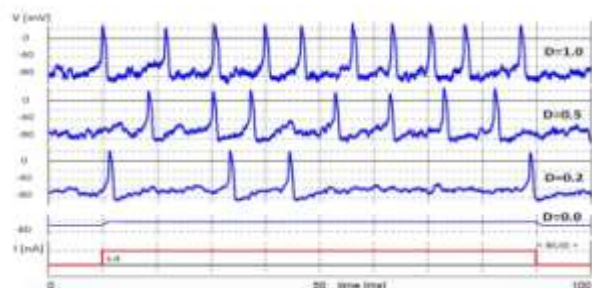
These are completely deterministic situations as you only will find them in mathematics or with computer simulations – but never in real life.



The recordings on the right are obtained with addition of a tiny noise current ( $D=0.01$ ). Four out of ten previously subthreshold stimuli have then been generating an action potential.

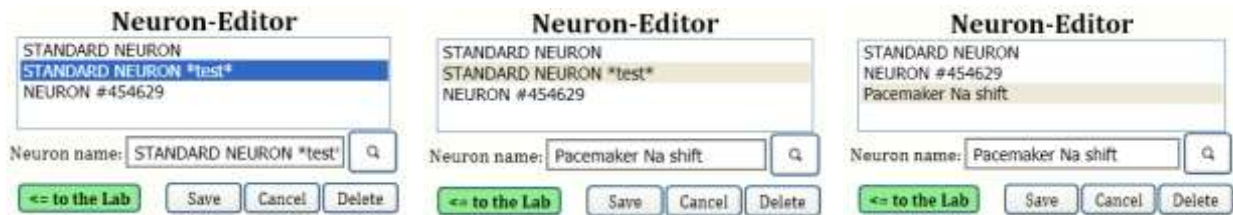
The second example illustrates, again with the Standard Neuron, the induction of spike activity of increasing firing rate in response to a deterministically clearly subthreshold stimulus - simply by addition of noise of increasing noise intensity  $D$ .

Indeed, with sufficiently strong noise spiking can even be induced without an additional current stimulus.



#### 4.4 SAVE your own Neurons

When you have changed a parameter of one of your neurons the neurons' name will appear in the selection box with the extension \*test\* - what here is shown with an example from the Standard Neuron (on the left) what usually will be the first step. You can go the current or voltage clamp lab to check the effects of the parameter changes.



In case that you want to save your Standard Neuron with the altered parameter values you have to type in another name, here "Pacemaker Na Shift" (according to the changes made in 4.2.1). The parameters of the Standard Neuron cannot be changed.

In case that you have changed the parameters of any one of your other neurons you will be asked whether this neuron shall be replaced by the new one or whether you want to save it under a different name.

In any case, after pressing the SAVE button, the new neuron will appear as the actually activated neuron in the selection box.

**Please note:** The parameter files of all neurons in the list will be saved with the extension ".VAR" in a specific folder "**sim-original**". With all more recent Windows versions (**Vista, Win7 and Win8**) you will find the folder "sim-original" in "**C:\ProgramData\Viphy\SimNeuron II\Files**". If you cannot see the folder "C:\ProgramData\" in your Windows Explorer you have to type in "C:\ProgramData" in the address field of your Windows Explorer.

In **Windows XP** your "**sim-original**" folder will be located in C:\Program Files\Viphy\SimNeuron II\Files\" (in German: C:\Programme\Viphy\SimNeuron II\Files\").

If too many neurons have accumulated you can go "**sim-original**" to manually delete undesired neurons from the neurons list.

## 5. Pre-Settings

SimNeuron versions 2.3 and higher offer the possibility to select to which specific features of the program your students shall have access. This can be done in so-called pre-settings window which you can open from the labs via the SETTINGS button in the switch bank. The access to the pre-settings is password protected. The initially set password is "admin". You can change the password from the pre-settings window, clicking on the password button.

Pressing the SETTINGS button and entering the correct password opens a window as shown in the figure below. There you will find a list of different features to which you can give access ("Yes") or which you may protect ("No"). The presetting in this figure are those as initially set. On the right, additional explanations to each point will appear as shown here for the last point. Explanations to the other points are given below.

SimNeuron Pre-settings	Description	
Open the lab with a randomly generated neuron. (on "No" the "Standard Neuron" will appear) <input type="radio"/> Yes <input checked="" type="radio"/> No	On "Yes", in the current -clamp lab two buttons will appear in the right lower corner of the current display which allow to switch from conventional step-like current injection to ramp-like current stimuli, e.g. to examine eventual accommodation effects.	
Allow to get randomly generated neurons (obtained with right mouse click on the lab cartoon) <input checked="" type="radio"/> Yes <input type="radio"/> No		
randomly generated Neurons with Noise? <input type="radio"/> Yes <input checked="" type="radio"/> No		
Allow to access to the "Neuron Editor" (also to generate new neurons) <input checked="" type="radio"/> Yes <input type="radio"/> No		
Overtake new neurons into the pre-settings list? (to reappear on the next program start) <input checked="" type="radio"/> Yes <input type="radio"/> No		
Allow to display conductances <input checked="" type="radio"/> Yes <input type="radio"/> No		
Allow to display currents separately <input checked="" type="radio"/> Yes <input type="radio"/> No		
Show reset Button (Initial settings) <input type="radio"/> Yes <input checked="" type="radio"/> No		
Allow switching to current ramp <input checked="" type="radio"/> Yes <input type="radio"/> No		
<input type="text" value="change password"/>		
<input type="button" value="CANCEL"/>	<input type="button" value="OK"/>	<input type="button" value="SAVE"/>

### SimNeuron-Presettings:

#### 1) Open the lab with a randomly generated neuron?

Here you can decide what kind of neuron will appear on program start. If "Yes" is selected you or your students will get a neuron with randomly chosen parameter values. Selecting "No" will open SimNeuron with the "Standard Neuron" which always will be the same and cannot be changed.



Please note: You will in any case have access to the “Standard Neuron which will appear on the top of your list of neurons in the drop down menu opening with click on the current neuron’s name.

## 2) Allow receipt of randomly generated neurons?

When this switch is set to “Yes” you can get additional neurons with random parameter values clicking with the right mouse button on the schematic drawing of the experimental set-up in the lower left corner of the labs. If this switch is set to “No” the possibility receiving new neurons is blocked.

## 3) Randomly generated neurons with noise?

selecting “Yes” means that randomly generated neurons include a noise term. This is not only to let the recordings appear more realistically. Also threshold of action potential generation and spike timing will exhibit some variability. For deterministic simulations with exactly reproducible reactions on identical stimuli, this switch should be set to “No”.

## 4) Allow access to the “Neuron Editor”

In case that this switch is set to “Yes” you or your students, respectively, will be able to open the “Neuron Editor” via the corresponding button in the SimNeuron voltage- and current-clamp laboratories. Selecting “No” blocks the access to the “Neuron Editor”.

The “Neuron Editor” shows the full equations and all parameter values of the current neuron. It also allows changing the neuron parameters thereby generating new neurons with different properties that can be saved in the current list of neurons.

## 5) Overtake new neurons into the pre-settings list?

If this switch is set to “Yes”, new neurons that have been generated during the current session will be overtaken into the list of preset neurons to appear in the next session. If the switch is set to “No”, new generated neurons will be deleted on program exit so that the original list of neurons will be preserved.

Of course, this switch is only of relevance when one or both of the switches above (receipt of randomly generated neurons or access to the neuron editor) are activated.

**Additional note:** If too many neurons have accumulated you can manually delete undesired neurons from the neurons list. You will find the list of neurons in the subfolder “**sim-original**”.

**Attention:** In Win Vista, Win7 and Win8 this subfolder is NOT located in "C:\Programme\Viphy\SimNeuron II\Files\" (due to restricted access) but in "C:\ProgramData\Viphy\SimNeuron II\Files\". If you cannot see the folder "C:\ProgramData\" in your Windows Explorer you have to type in "C:\ProgramData\".

## 6) Allow to display conductances

Selecting “Yes” will bring a check box on the screen in both the current- and voltage-clamp lab which can be activated also to display the time course of Na and K conductances – which, of course, cannot directly be seen in real experiments. On “No” this option is blocked and the check boxes will not appear.

## 7) Allow to display currents separately

If “Yes” is selected check boxes will appear which allow to display the voltage dependent Na and K currents separately. This will not be possible when the switch is set to “No”. Then, the check boxes will be hidden.

## 8) Show Reset Button (Initial Settings)

On “yes” a button will appear in the right upper corner which allows reinstalling the initial settings (scaling and stimulus adjustments as after program start).

## 9) Allow switching to current ramps

On “yes”, in the current-clamp lab two buttons will appear in the right lower corner of the current display which allow to switch from conventional step-like current injection to ramp-like current stimuli, e.g. to examine eventual accommodation effects.

### Buttons:

**Password:** opens a window to change the password

**Cancel:** closes the pre-settings without considering currently made changes

**OK:** overtake the changes for the current experiments

**SAVE:** preserve the changed pre-settings also for the next program start