PhysioLAB edu ™: An Interactive, Modeling and Simulation System for Learning and Research in Biomedicine

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Abstract:

PhysioLAB edu™ is an educational and research tool that provides numerical experiments within a simulation system. It uses simulations of mathematical models to represent how real biological systems work. Using this system makes possible the integration of physiological systems. This computing system is an object-oriented program based on a unifying theoretical framework with a common formalism for phenomena at different levels of a hierarchical system. Students may interactively investigate the basic mechanisms of physiological phenomena. Faculty and engineers may use *PhysioLAB edu* for teaching and research (because their own models can be inserted in the time and space algorithm that allows traversing levels of organizations).

I. Aim of the *physiolab edu* System: Integrative Physiology

The primary aim of *PhysioLAB edu* is to describe the phenomena of biological systems, from elementary physiological mechanisms to global function, in such a way that:

1. *A unique conceptual framework* with general principles and concepts specific to biology are used, which provides:

    The same common bases for interpretation of biological phenomena;

    The same bases for, ultimately, improving biological knowledge.

    It will be shown that this is obtained using a specific formalism (the S-Propagator Formalism) to traverse levels of organization, and to study couplings between sub -systems in the organism.

2. The results of simulations under the usual form of mathematical curves simultaneously associated with what happens in physical reality, e.g. injection of current at a given point across the membrane simultaneously with the recorded potential curve (Fig 1).

3. The system allows analysis and understanding of the role of internal and environmental parameters on the phenomena (e.g. temperature, friction). These parameters are presented in a panel with their default values. It is possible to quantitatively observe the role of experimental conditions, i.e. the role played by controlled parameters, on the physiological process (e.g. ion species, holding potential); their values can be continuously chosen using a scrollbar and results are simultaneously presented.
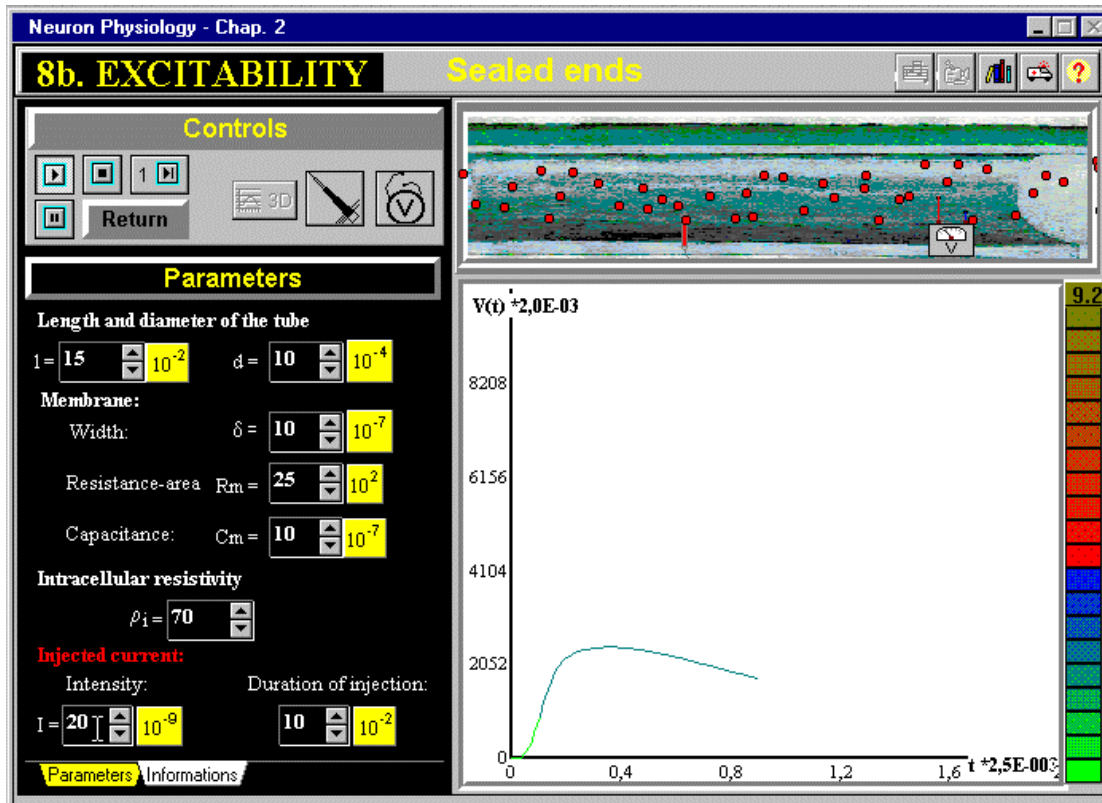
Figure 1: An example of screen that shows a virtual experiment in the Neuroscience course (cell physiology).

These three points are developed in the following sections.

II. First step: Abstract representation of the biological system

The first step in learning physiological systems, more generally biological systems, is to isolate this system from others. This means to be able to identify all of its couplings with the other subsystems of the organism. In terms of elementary functional interactions from structural units that are the sources to the others that are the sinks, a functional order can be introduced using specific properties of these interactions, i.e. non-symmetry and non-locality. In this abstract representation, a biological system may be viewed as in Fig.2a, where the physiological function is defined by the time scale of the dynamics, leading to functional hierarchy. The structural units that contribute to this function are distributed along the space scale of the structure.

PhysioLAB edu is a computing system, a research simulation tool using object oriented programming based on a unifying theoretical framework that uses a common formalism for phenomena at different levels of a hierarchical system. Fig. 2b shows a screen of the module which organizes biological data in terms of functional interactions, i.e. which gives raise to the mathematical graph of the biological system. Using this complex hierarchical graph provides the biological system to study with its own functional interactions and the couplings with environmental subsystems, e.g. the cerebellum[1]. This rigorous approach allows the user to see how the biological system is structurally and functionally organized. Consequently, identifying

state variables and parameters of the system is made easier. At least, they will be the same for all the users.
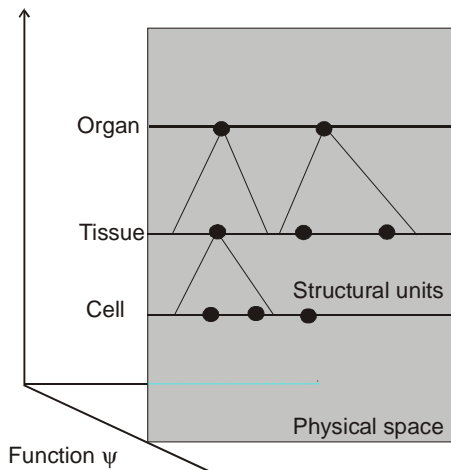

Figure 2: a) Top. A biological system represented in terms of space scales (structural hierarchy), time scales (functional hierarchy) and structural units. The grey plane represents a physiological function, e.g. ψ, and its levels of structure. The lowest level is the physical space. b) Bottom. The organism conceived as a set of interactions between levels of structural organization. The mathematical graph shows the biological system as if it was viewed from the top to the bottom for the selected function: structural units are balloons included one in the other. This inclusion is represented using a hat in Fig.2a. Each balloon corresponds to a level, and their inclusion means that a given structure belongs to the structure hierarchically above.
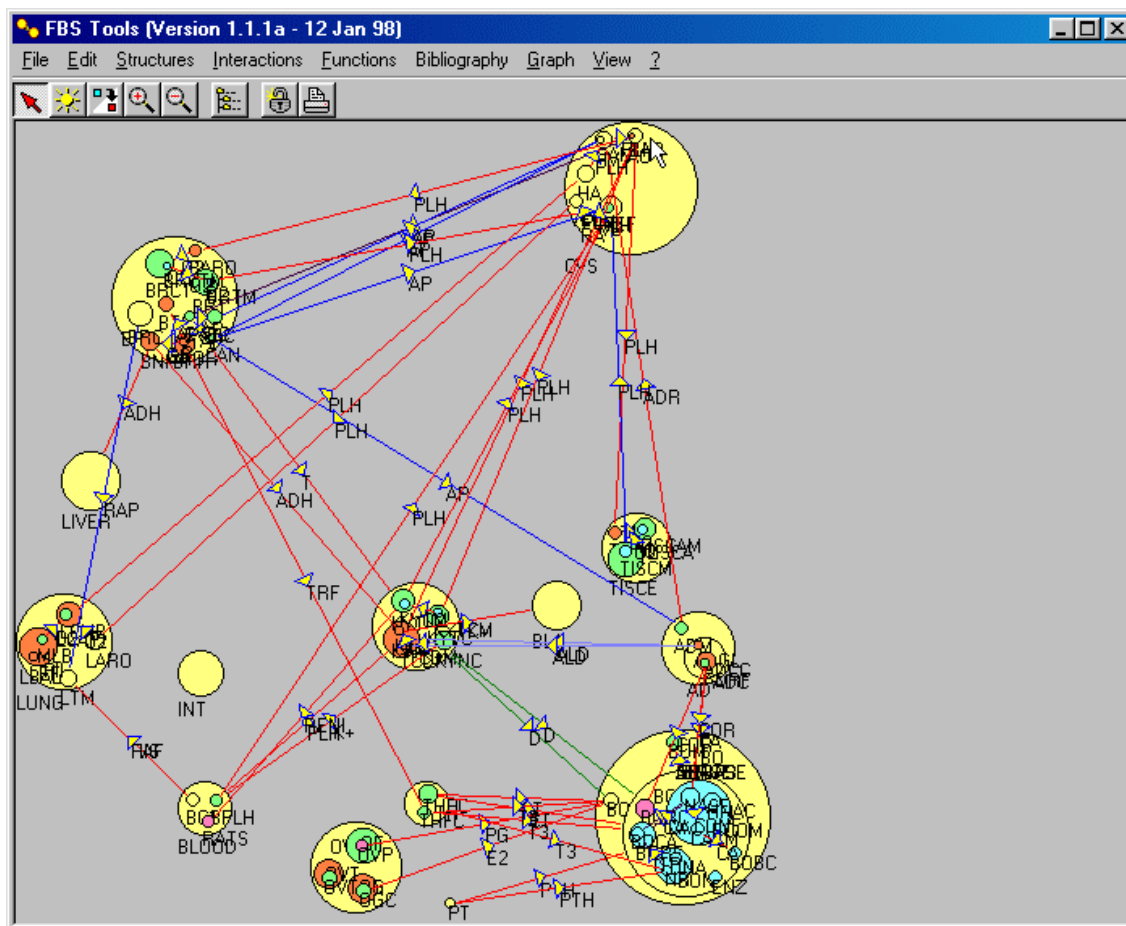
III. Second step : Dynamics of the biological system
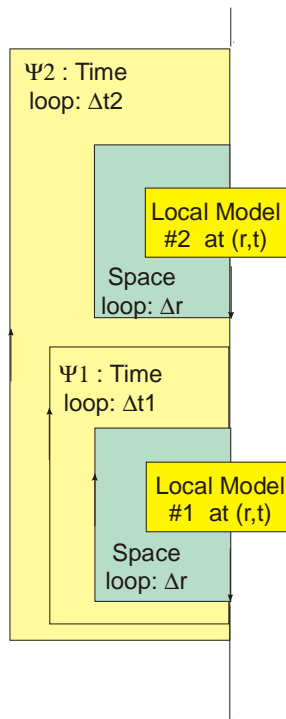
Figure 3: Algorithm corresponding to the hierarchical system in Fig.2a.

Once the biological system has been identified, which means its couplings with other subsystems clearly established, the dynamics of the system may be analyzed. The state variables are the functional interactions ψ that depend on space and time, e.g. the membrane potential of neurons that are located at point r in the space of neurons, and measured at time t. Because of the distribution of the physiological functions along the time scales (e.g. $\psi1$ and $\psi2$), the computing algorithm involves the local model at (r,t) inside the time loop that corresponds to its own time scale (Fig.3). Thus, from Fig.2a, it is clear that each function is mathematically solved in its time loop, and that the functional hierarchy corresponds to the hierarchical inclusion of time loops.

Now, because a given function works in a given structural hierarchy (gray plane in Fig.2a), formalism is needed to traverse the levels of structure from one point to another (space loop, see Fig.3). Such formalism has been conceived[2] (S-propagator) which is based on the propagation of fields submitted to non-local and non-symmetric operators. Operators correspond to the specific models that are usually studied in biosciences. Although algorithm is general in terms of time loops and of non-local field interpretation for the functional interactions, traversing levels of structural organization needs specific local models chosen by the user.

The general principles on which the S-propagator formalism is based lead to the integration of the different physiological functions, e.g. the nervous system and the respiratory system. It is then possible to demonstrate the interrelations between hierarchically organized sets of dynamical systems[3] ; such interrelations are a fundamental, defining feature of complex physiological systems like the nervous system, and of biological organisms in general.

IV. Architecture of the computing system: From the local models to the global system

The computing system *PhysioLAB edu* integrates the local models that are objects in the framework of object oriented programming. Specific models are chosen in the model database, and their parameters may be modified depending on experiment. The program is organized as shown in Fig.4. The numerical engine solves partial differential equations (field equations) and the associated differential equations that correspond to the local models. There are three Graphical Interface Users that are devoted to, respectively, inputs and parameters of the local models, parameters of both the global model and the engine, and graphical outputs.

In the next section some examples of the local models are given, organized in a series of books for education and research. They are then integrated within the program *PhysioLAB edu*. Of

course, inserting local models inside the global one through *PhysioLAB edu* needs the conceptualization of the problem which can be done using the module "topology" (see the above second section).
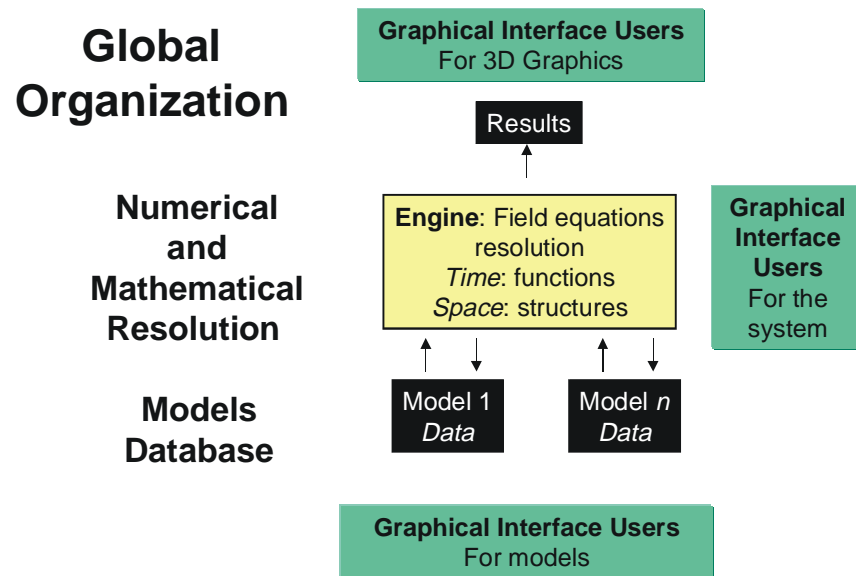

Figure 4: Organization of the program that finds the solution of the global, integrated model of a given physiological function.

V. Examples: How the formalism applies in learning

First Virtual Experiment: Membrane Potential of a Neuron. The neuron is considered as a system from the perspective of ion transport. There are permeant ions and non-permeant ions, including non-diffusible macro-ions. Ion concentrations (potassium, sodium, chloride and another anion A) are measured inside and outside the cell. The computing system may give an answer to several questions: (i) Is the neuron in electrochemical equilibrium? (ii) Is there space-charge neutrality? (iii) What is the direction of moving until equilibrium? (iv) What is the distribution of ions at the final equilibrium? (v) In this final state, is there osmotic equilibrium?

An answer to all these questions is given on the screen (Fig. 5) in which the default values into the new given values have just to be changed. The sequence of operations are the following:
1. Go to the *table of Contents;*
2. Click on …*Donnan potential*: read on the blackboard to check that what you though about this problem is correct; then
3. Click on *simulation*;
4. Click on the tab *informations* and read it; click on the *ambulance button* to check the measurement units;
5. Click on the tab *Data and Default values*;
6. Change the values:
    in compartment (in), box *Anion* into 50; box *cation* into 150,
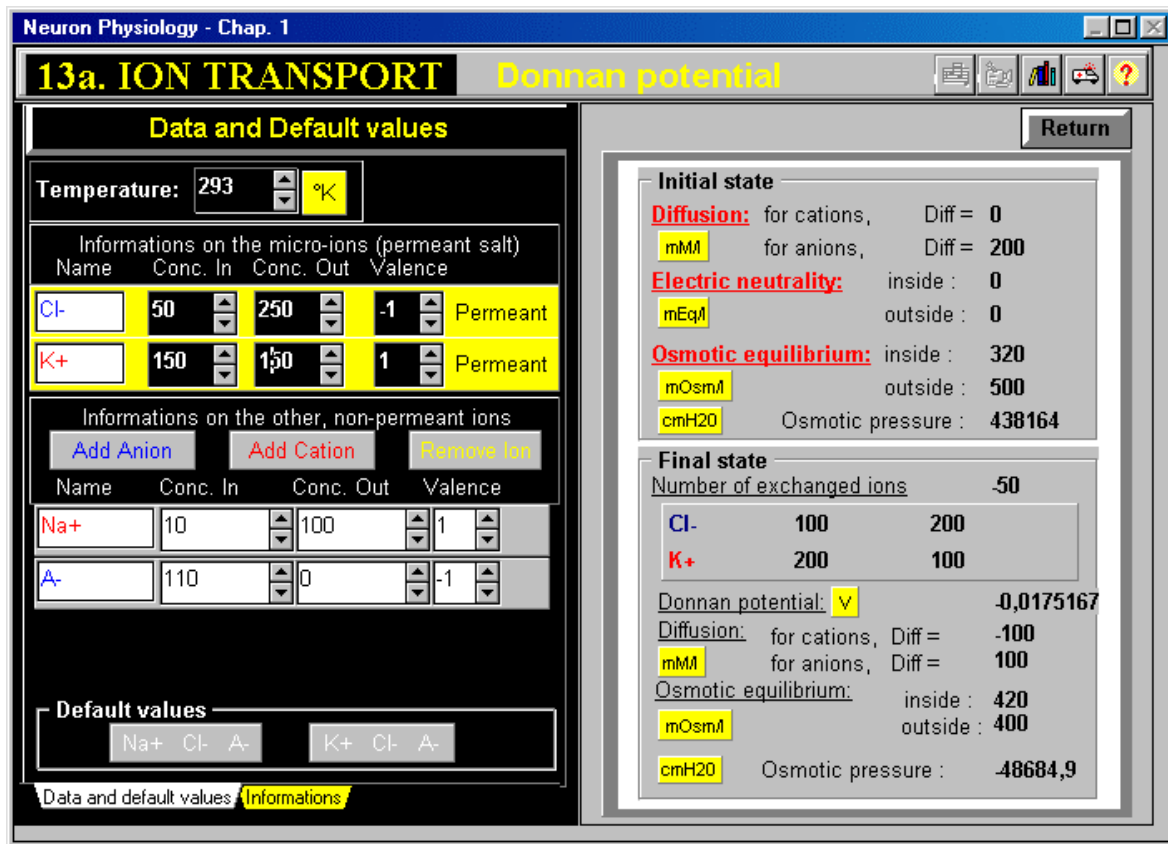
Figure 5 : The screen which presents the calculations for ion membrane transport. On the left: data and informations; on the right: results for chemical equilibrium (Donnan potential, osmotic equilibrium).

  in compartment (out), box *Anion* into 250; box *cation* into 150, remain *valence* to -1 and 1 respectively.

7. Click on *Add cation* in the panel below for *non-permeant ions*:
8. Put in the box *cation* the value 10 for compartment (in) and 100 for compartment (out);
9. Click on *Add anion* in the same panel, and
10. Put in the box *anion* the value 110 for compartment (in) and 0 for compartment (out);
11. Inspect the calculated data on the view screen.

As soon as the last data is entered, the screen (Fig. 5) is obtained. The value of the membrane potential (Donnan potential) is – 17.5mV

Second Virtual Experiment: Initiation and Propagation of the Action Potential. In this virtual experiment, membrane characteristics such as Nernst potentials calculated from ion concentrations, ion conductances, effect of temperature, etc., can be modified to observe the changes in initiation and propagation of the action potential (Fig.6). Time courses of membrane potential, opening and closing functions for sodium and potassium, are visualized simultaneously as a function of distance. PDEs are solved in real time, and the above parameters may be varied at any time.
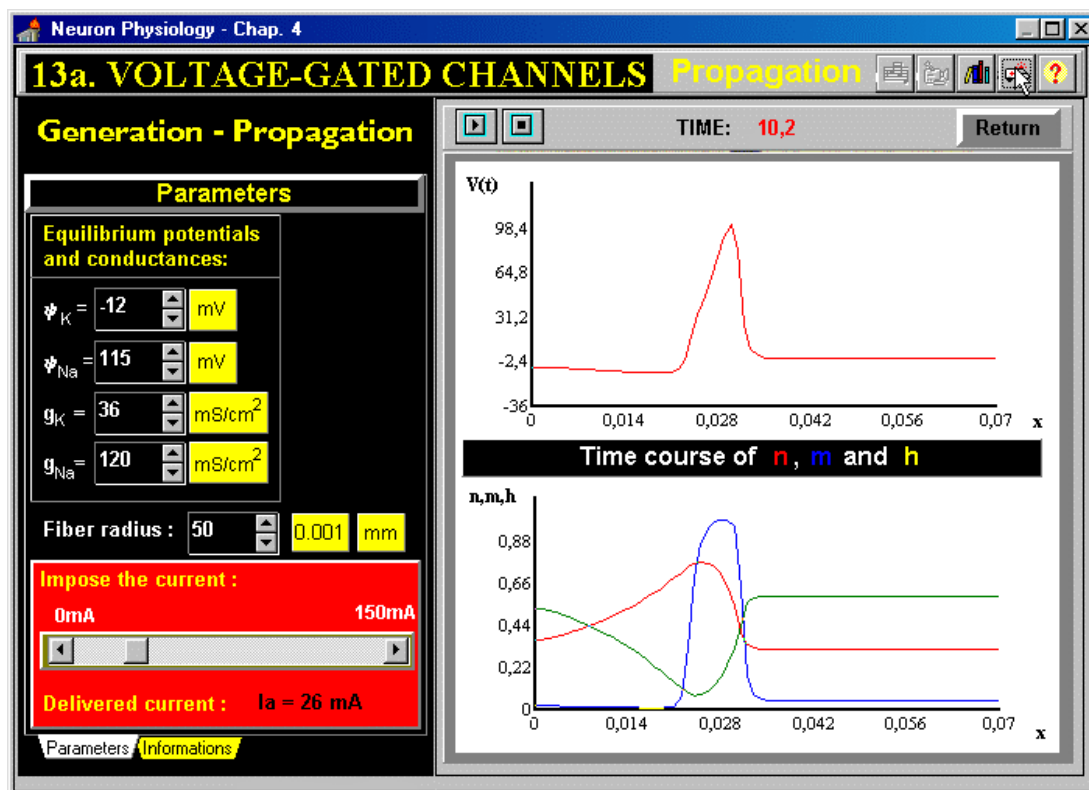
Figure 6 : Initiation and propagation of the action potential. Membrane parameters can be varied to observe their effect on initiation and propagation, as well as ion concentrations, temperature.
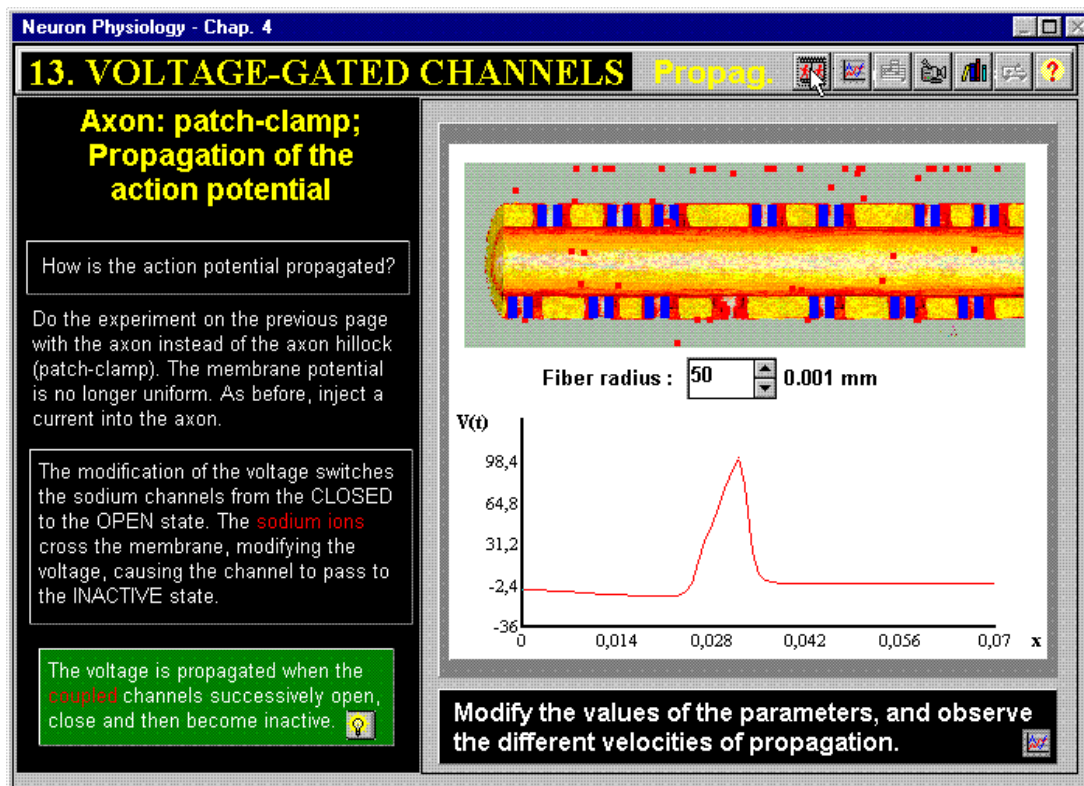

Figure 7: This screen shows the main feature of PhysioLAB edu. The two synchronized figures represent the same phenomenon of propagation: what happens in the physical reality (opening and closing of channels, top), and the dynamics of the membrane potential.

Once the phenomenon of propagation has been observed from two points of view (Fig.7), in the physical space and on the oscilloscope, it is possible to vary the parameters that are basic for the phenomenon, e.g. the Nernst potentials. This can be done using the virtual experiment shown in Fig.6.

VI. Discussion and Conclusion

PhysioLAB edu is an educational and research tool that provides numerical experiments within a simulation system. It uses simulations to represent how real biological systems work. Using this system makes possible the integration of physiological systems in a specific theoretical framework (G. Chauvet, 1996) that introduces the hierarchical organization of physiological functions in terms of the structural organization. The global dynamics then result from integrated specific models given by the user. *PhysioLAB edu* may help students in learning, and faculty and engineers in teaching and research.
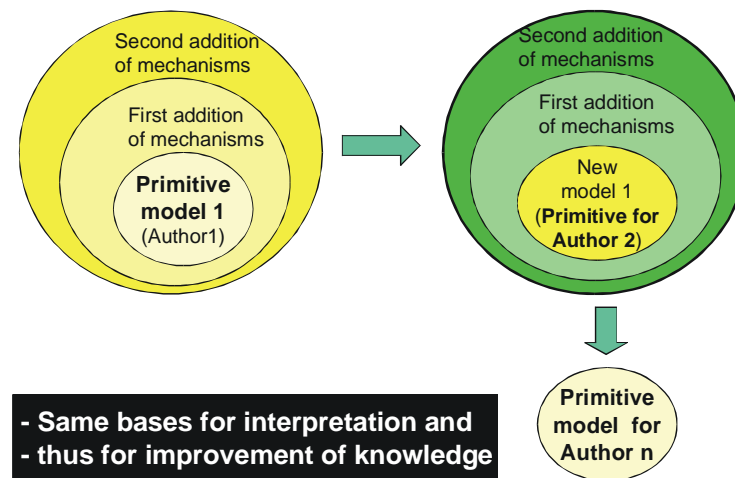
Figure 7: This diagram explains how knowledge on biological systems could be constantly improved. Different authors add new physiological mechanisms identified using experiments.

There are at least two main features that emerge from this system.

First, students may interactively investigate the basic mechanisms of physiological phenomena: 1) They can understand how the proposed phenomena emerge from the hierarchical construction of living tissues and from their anatomical location. 2) They can discover the couplings between mechanisms through simulation of classical experiments as actually made by the original authors. 3) They can use intensive interaction between the student and the computer through a friendly and attractive interface. The experiments work as in a real lab on the basis of animations and simulations all driven by mathematical models. Modules in the *PhysioLAB edu* neurocell program correspond to specific parts of the body, the brain, the respiratory, the cardiovascular, and the renal systems.

Second, and from a more general point of view, the common algorithm based on the field formalism provides the tool that allows integration of specific user's models in a common theoretical framework. This is a necessary condition to study couplings between subsystems. The specific models are either chosen in a database, or conceived by the user. They may be either complex or simple depending on the experiment to be interpreted. Because of this unique feature, we may imagine the biological knowledge constantly improved by different authors working on the same database (Fig.7). They will make the specific models more and more precise on the same background.

Faculty and engineers may use *PhysioLAB edu* for (i) teaching (because the corresponding simulations can be used for solving problems given by the teacher), and (ii) research (because their own models can be inserted in the time and space algorithm that allows traversing levels of organizations). The aim of this system is to make possible integrative physiology by accessing model database and model integration without programming

References:
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2.   G.A. Chauvet, S-propagators: A formalism for the hierarchical organization of physiological systems. Application to the nervous and the respiratory systems. *Int. J. General Systems*, **28(1)**, pp. 53-96 (1999).
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