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The dynamic clamp comes of age

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The dynamic clamp uses computer simulation to introduce artificial membrane or synaptic conductances into biological neurons and to create hybrid circuits of real and model neurons. In the ten years since it was first developed, the dynamic clamp has become a widely used tool for the study of neural systems at the cellular and circuit levels. This review describes recent state-of-the-art implementations of the dynamic clamp and summarizes insights gained through its use, ranging from the role of voltage-dependent conductances in shaping neuronal activity to the effects of synaptic dynamics on network behavior and the impact of *in vivo*-like input on neuronal information processing.

The term dynamic clamp refers to a variety of hardware and software implementations used to create artificial conductances in neurons. Since its introduction more than ten years ago [1–3], the dynamic clamp has become a standard tool of electrophysiology, used in a wide variety of experimental preparations to address a host of different issues. This review describes how the dynamic clamp creates an artificial conductance, provides an overview of some of the different dynamic-clamp systems currently in use and discusses what can and has been achieved using the technique.

What is the dynamic clamp?

In contrast to conventional voltage- or current-clamp recording configurations, the dynamic clamp effectively alters the conductance of a neuron [1,2]. It does so by using the measured membrane potential to control the amount of current injected into a neuron. To simulate a particular conductance, the dynamic clamp computes the difference between the measured membrane potential and the reversal potential for that conductance, multiplies this 'driving force' by the desired amount of conductance, and injects the resulting current into the neuron. Accurate dynamic-clamp performance requires uninterrupted, rapid sampling of the membrane potential and fast computation of the current to be injected. If the sampling and computation are fast enough, the electrophysiological effects of any set of ion-conducting channels can be reproduced as if these were located at the site of voltage measurement and current injection.

Any time- or voltage-dependent conductance that has been described mathematically and can be simulated on a computer can be introduced into a neuron using the dynamic clamp. For a voltage-dependent conductance, the injected current is determined by a set of differential equations that describe the voltage and time dependence of the conductance. For a synaptic conductance, the current injected by the dynamic clamp is computed on the basis of presynaptic input that is either recorded from another neuron, or generated by a model neuron or by a descriptive model of typical *in vivo* input.

Dynamic-clamp implementations

Obtaining sufficiently high update rates in the first dynamic-clamp implementations of the early 1990s pushed the limits of computer and data acquisition board technologies available at that time. As a result, some of the earliest dynamic-clamp programs were written in machine language [1,2] and used look-up tables [3], and some implementations used digital signal processing (DSP) boards to achieve the required speed [4]. Today, computers and boards are so fast that hardware speed is no longer a significant issue, and many different dynamic-clamp systems have been developed and used in several laboratories around the world. These systems vary considerably in their front-end user interfaces, in how readily programmable they are, in how many different conductances can be simulated, in how many neurons can be studied simultaneously, in whether they display and save voltage and current traces online, and in their cost. Our conservative estimate is that there are at least 20 different dynamic-clamp setups in use in laboratories around the world today, and many more papers than can be cited here have been published with some version of dynamic-clamp implementation. Table 1 lists several of the dynamic-clamp systems presently in use to illustrate the diversity of approaches, hardware, and features. Because computers and boards change so quickly, this list provides only a snapshot of the present situation.

Currently available implementations of the dynamic clamp include applications that run under the Windows or Real-Time Linux operating systems, systems that use embedded processors or DSP boards, and versions that use analog devices. The advantages and disadvantages of these different approaches are outlined briefly below.

Windows-based applications

Windows-based dynamic-clamp systems typically achieve update rates of 2–20 kHz, depending on the computational load for the particular conductances being simulated [5–7]. This is fast enough for most purposes, but extremely fast conductances, such as those of fast Na^+ currents, can only be approximated crudely. An additional problem stems from the fact that

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Table 1. Recent examples of dynamic-clamp implementations[a]

	Windows-based	Real-time Linux-based		Embedded processor or DSP	Analog device	
References	[6]	[9]	[10]	[12]	[14]	Instrutech, ITC-18
URL	inls.ucsd.edu/~rpinto/	www.bu.edu/ndl/rtldc.html	www.neuro.gatech.edu/mrci/	NA	NA	www.instrutech.com
Programming language	C++	C, C++for user interface	MRCI modeling language, C	Real-Time LabView	NA	NA
Update rate[b]	10 kHz	20 kHz[d]	30 kHz	40 kHz	NA	50 kHz
Existing applications	Artificial conductances; artificial chemical or electrical synapses between up to four cells	Artificial conductances; hybrid two-cell networks; adding multiple compartments	Artificial synaptic inputs; hybrid two-cell networks	Artificial conductances; artificial chemical synapses; recording current–voltage curves	Artificial synaptic inputs	Artificial synaptic inputs
Number of channels[c]	Four in, four out	Two in, two out[d]	Two in, two out	Two in, one out	Four in, four out	Four in, four out
User interface	Graphical	Graphical	Command line	Graphical	NA	NA
Saves traces?	No	Yes	Yes	Yes	NA	NA
Displays traces?	No	Yes	No	Yes	NA	NA

[a]Abbreviations: DSP, digital signal processing; MRCI, model reference current injection; NA, not available.
[b]Update rates vary depending on the computational load. Updates rates given here are maximum values of published versions of the systems and will increase with time.
[c]Channel numbers given here are those of published versions of the systems. Most systems can be modified to handle larger channel numbers if different hardware is used.
[d]Newer, unpublished versions of this system can achieve update rates of up to 40 kHz, and can handle as many as 16 input and 2 output channels (J. White, pers. commun.).

any Windows-based program must deal with operating system interrupts through which Windows distributes processor time between different tasks. These can lead to discontinuities and gaps in dynamic-clamp operation and prevent real-time performance, even at low update rates.

The Windows-based dynamic clamp described by Pinto and colleagues [6] uses a Digidata 1200 board (Axon Instruments, http://www.axon.com) for data acquisition and digital-to-analog conversion. Because such boards are commonly used (and this dynamic-clamp software is available for free download from the developers), this particular implementation requires no more of a financial investment than that required for a standard electrophysiology rig.

Real-Time Linux-based applications

Recently developed versions of the dynamic clamp that operate under Real-Time Linux avoid the interrupt problem of a Windows-based system and can achieve update rates of 20–50 kHz, depending on the data acquisition board [8–10]. At the moment, the installation and operation of the real-time operating system requires considerable expertise, which can deter some users. However, with several laboratories developing more user-friendly Real-Time Linux-based dynamic-clamp systems, the installation and use of these systems is rapidly becoming easier.

Embedded-processor and DSP-based systems

Update rates of 20–50 kHz can also be achieved by using an embedded processor or DSP board [4,11–13]. These devices can be controlled by a host computer and programmed through a graphical programming language with a user-friendly interface [12] or through Real-Time Workshop (The MathWorks, http://www.mathworks.com), but these advantages literally come at a high price. The costs for the additional hardware, necessary drivers, and compiler software can be between US$5000 and US$10 000.

Analog devices

For some applications, the dynamic clamp can be implemented using analog circuits that perform the basic subtraction and multiplication operations needed to convert a desired conductance and a measured potential into an injected current [14]. These analog circuits are commercially available (e.g. SM-1 from Cambridge Conductance, http://homepage.ntlworld.com/cambridge.conductance; or ITC-18 from Instrutech Corporation, http://www.instrutech.com). The advantage of an analog approach is its high speed, which is essentially instantaneous on the scale of typical membrane and synaptic time constants. However, the basic analog system only makes the conversion from conductance to injected current. For any application other than the simulation of a constant conductance, these systems must be driven by a digital computer programmed to calculate the desired conductance and drive the analog circuitry. As a result, analog systems are most useful in cases where synaptic, rather than voltage-dependent, conductances are being simulated.

Applications of the dynamic clamp

Uses of the dynamic clamp have been divided here into five broad categories: simulation of voltage-independent conductances, simulation of voltage-dependent conductances, simulation of synapses between neurons, construction of biological–computer hybrid circuits, and simulation of *in vivo* synaptic input. For each of these categories, a single example from the many possibilities in the literature has been chosen to illustrate what can be achieved and what has been learned using these approaches. Additional selected studies using the same dynamic-clamp approach are briefly summarized for each category.

Effects of voltage-independent conductances

Simulating a voltage-independent conductance is the simplest thing that can be achieved with the dynamic clamp (Figure 1a) but, nevertheless, it is useful for studying the effects of leakage conductances or ligand-gated conductances on neuronal dynamics. Figure 1b provides an example in which a dynamic clamp was used to duplicate the effect of a ligand-gated conductance with a reversal potential of −75 mV in a neuron of the crustacean stomatogastric ganglion to study the effects of a voltage-independent GABA conductance [2].

Dynamic-clamp conductances act in parallel with the normal membrane conductances of the neuron, and the interaction between the added and existing conductances is what makes such manipulations interesting. In the example shown in Figure 1b, current pulses of constant amplitude were introduced to show that the dynamic clamp was modifying the conductance of the neuron (Figure 1b, bottom) in exactly the same way as a bath application of GABA (Figure 1b, top). The dynamic clamp mimics both the GABA-induced hyperpolarization and the reduction in the voltage response to constant-amplitude current pulses caused by the GABA conductance. In a related approach, the dynamic clamp has been used to add artificial GABA conductances in thalamocortical relay cells to elucidate the role of GABA-mediated inhibitory postsynaptic potentials (IPSPs) in rebound burst firing and burst inhibition [15,16].

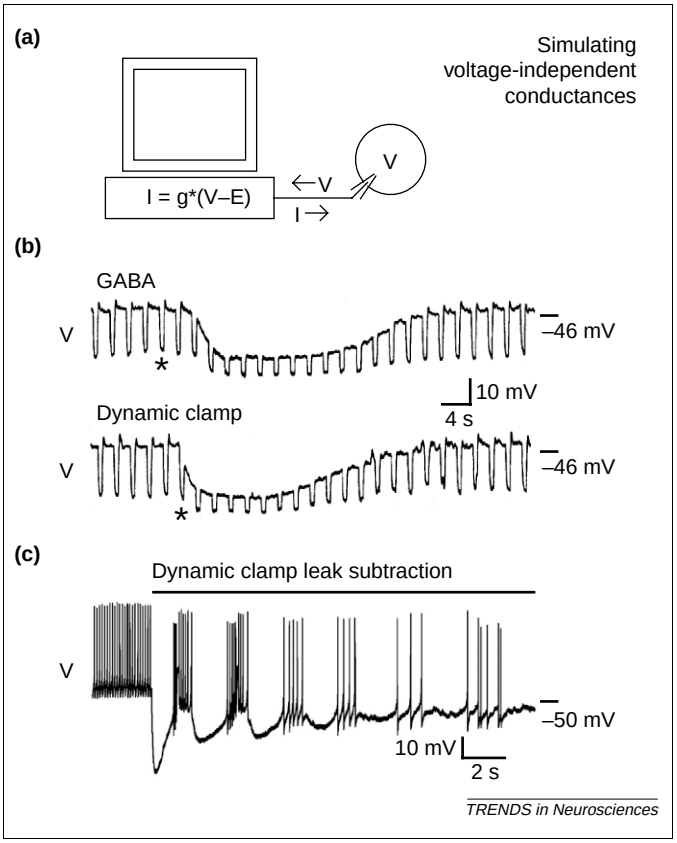

Figure 1. Using the dynamic clamp to simulate voltage-independent conductances. **(a)** Schematic of the experimental configuration. The dynamic clamp computes the current, I, flowing through a voltage-independent conductance, g, as g multiplied by the instantaneous driving force, V–E, where E is the reversal potential and V is the membrane potential. In every cycle of dynamic-clamp operation, V is measured and fed into the computer, I is computed based on the momentary value of V, and I is injected into the cell. Voltage measurement and current injection can be made through the same electrode with discontinuous clamp techniques, or through two separate electrodes. **(b)** Voltage traces recorded from a cultured crab stomatogastric neuron during 30 s bath application of 0.1 mM GABA (top) and during dynamic-clamp injection of an exponentially rising ($t = 5$ s) and falling ($t = 15$ s) GABA conductance with a reversal potential of -75 mV (bottom). The starts of bath and dynamic-clamp application are indicated by asterisks. During both runs, current pulses of -0.5 nA were applied every 3 s to illustrate the change in input conductance. Adapted, with permission, from Ref. [2]. **(c)** Voltage trace from a leech heart interneuron before and during injection of a negative leak conductance of -6 nS with a reversal potential at 0 mV. The leak subtraction compensates for the effect of sharp microelectrode penetration, which suppresses bursting. Adapted, with permission, from Ref. [17] © (2002) by the Society for Neuroscience.

In addition to being added, conductances can, with some restrictions, be subtracted using the dynamic clamp. Figure 1c shows an example. The leakage conductance introduced by the electrode penetration required for intracellular recordings made with sharp electrodes is a potential source of distortion of the natural activity of the recorded neuron. Figure 1c shows an example in which the dynamic clamp was used to simulate a negative conductance designed to cancel out the impact of the leakage introduced by electrode penetration [17]. Addition of an artificial leak conductance had been shown previously to switch leech heartbeat interneurons from an active state with high-frequency bursting to an inactive state [18]. Because of this sensitivity of bursting to additional leak conductance, the electrode leak was removed by the dynamic clamp. The bursting activity that is the natural mode of operation for this neuron was revealed only after the leakage conductance introduced by electrode penetration was subtracted using the dynamic clamp.

Taken together, dynamic-clamp studies that simulate voltage-independent conductances in different preparations demonstrate important roles for seemingly simple leak and ligand-gated currents in shaping neural activity. The importance of voltage-independent conductances is further supported by reports that dynamic-clamp simulated leak current can increase motoneuron spiking in the mammalian spinal cord [19] and that adding a Ca^{2+} window current or subtracting leak current can render thalamocortical neurons bistable [20].

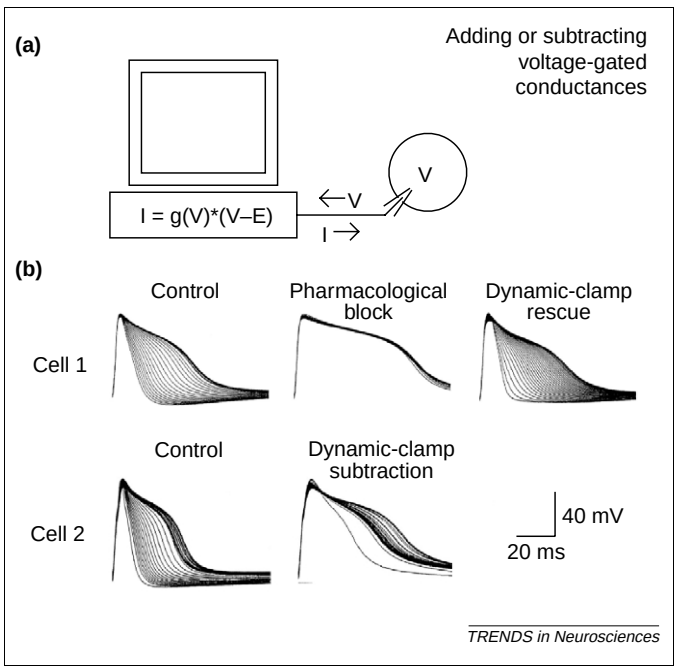

Figure 2. Adding or subtracting voltage-dependent conductances. **(a)** Schematic of the experimental configuration. The dynamic-clamp current is computed as in Figure 1, but in this case the conductance, g, varies with time and depends on the membrane potential, V. **(b)** Each panel shows 65 superimposed spikes from an *Aplysia* R20 neuron in response to 7 Hz current pulse injection. In control conditions, the action potential is initially narrow and broadens during the spike train (top-left). Spike broadening is abolished in 50 mM tetraethylammonium (TEA) and 10 mM 4-aminopyridine (4-AP; top-middle) and rescued when an A-type and a delayed-rectifier K^+ current are added with the dynamic clamp (top-right). In a different cell (bottom), the action of the blockers was approximated by subtracting these two conductances with the dynamic clamp. Adapted, with permission, from Ref. [21] © (1996) by the Society for Neuroscience.

Effects of voltage-dependent conductances

The dynamic clamp can be used to introduce voltage-dependent conductances into a neuron (Figure 2a), which is useful for exploring the impact of different intrinsic membrane conductances on neuronal activity. Specific conductances already present in the ensemble of intrinsic conductances in the neuron can be augmented or decremented to reveal the role that they play in generating its particular pattern of firing. Used in this manner, the dynamic clamp supplements more traditional methods of blocking conductances pharmacologically because it allows for very specific targeting and very precise control of the amount of the modification being made on any conductance. In addition, non-native voltage-dependent conductances can be added to the natural complement of the neuron to see what novel dynamics can be generated.

Figure 2b provides an example of this type of manipulation [21]. Each panel shows 65 superimposed spikes recorded from an *Aplysia* R20 neuron responding to the injection of current pulses at 7 Hz. In control conditions, the action potential broadens during repetitive spiking (Figure 2b, top-left). This broadening was abolished when A-type and delayed-rectifier K^+ conductances were pharmacologically blocked because the initial spikes were already broad (Figure 2b, top-middle). Spike broadening was restored under the pharmacological block by adding these conductances back using the dynamic clamp (Figure 2b, top-right). This result clearly implicates A-type and delayed-rectifier K^+ conductances in the phenomenon of spike broadening. The dynamic clamp could also partially duplicate the effect of the pharmacological blockade when it was used to subtract these two conductances (Figure 2b, bottom).

Dynamic-clamp simulation of voltage-dependent conductances has been used in stomatogastric ganglion neurons to investigate the roles of transient K^+ currents and hyperpolarization-activated inward currents [22,23], to study the effects of a neuromodulatory peptide-elicited current on the output of a rhythmic network [24], to show that a slow K^+ conductance can underlie cellular short-term memory [25], and to demonstrate how the relative amounts of different Ca^{2+} and K^+ conductances can determine whether a neuron is silent, spikes tonically, or bursts [26]. Artificial voltage-dependent currents have been used in preparations as diverse as pancreatic β-cells [27,28], thalamocortical [29] and neocortical neurons [5], and hippocampal interneurons [11]. The dynamic-clamp studies in these systems have identified individual voltage-dependent conductances involved in subthreshold membrane resonances [5], high-frequency spiking [11], bursting [27–29] and delta oscillations [29], and have thus contributed considerably to our understanding of dynamic processes in these systems.

Building and modifying neuronal circuits with artificial synapses

Thus far, we have focused on applications in which the dynamic clamp is used to introduce or remove membrane conductances to assess their role at the single neuron level. The remaining examples show uses of the dynamic clamp for creating artificial synaptic conductances. In these applications, the neuron being dynamically clamped acts as the postsynaptic element, and another neuron or a computer model acts as the source of presynaptic input. Here, cases in which the presynaptic element is another neuron are considered. As illustrated in Figure 3a, this approach requires recording the membrane potential of the 'presynaptic' neuron and using it and the dynamic clamp to control current injection into the 'postsynaptic' neuron. A synapse in an existing circuit can be augmented or decremented to study its effect on network activity, or a simulated synapse can be introduced where none existed before, allowing for the construction and study of completely novel neural circuits. The dynamic clamp provides the experimenter with complete control over the strength and other properties of these artificial synapses.

Figure 3b shows an example in which a so-called 'half-center' oscillator was constructed by connecting two stomatogastric ganglion neurons with reciprocally inhibitory synapses that were simulated with the dynamic clamp [6]. To construct the half-center oscillator, the two neurons were first isolated and then connected by artificial

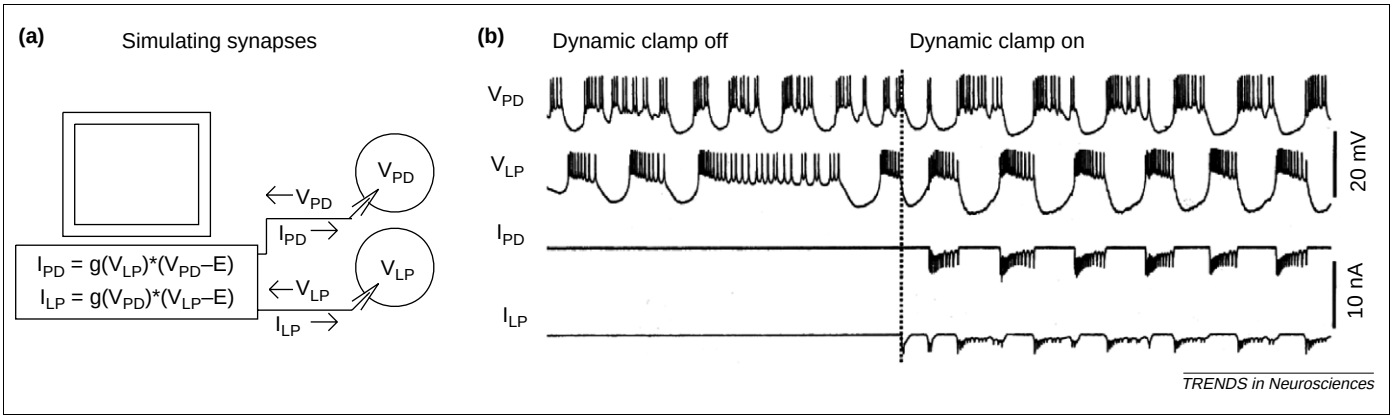

Figure 3. Creating artificial synapses between real neurons. **(a)** Schematic of the experimental configuration. The current that is injected into the postsynaptic neuron (I_{PD} or I_{LP}) is the product of the synaptic conductance, which depends on the membrane potential of the presynaptic neuron, and the driving force. **(b)** Voltage and dynamic-clamp current traces for a pyloric dilator (PD) and a lateral pyloric (LP) neuron of the lobster stomatogastric ganglion before and after the dynamic clamp was switched on. The artificial synapses induced the neurons to oscillate in antiphase. Adapted, with permission, from Ref. [6].

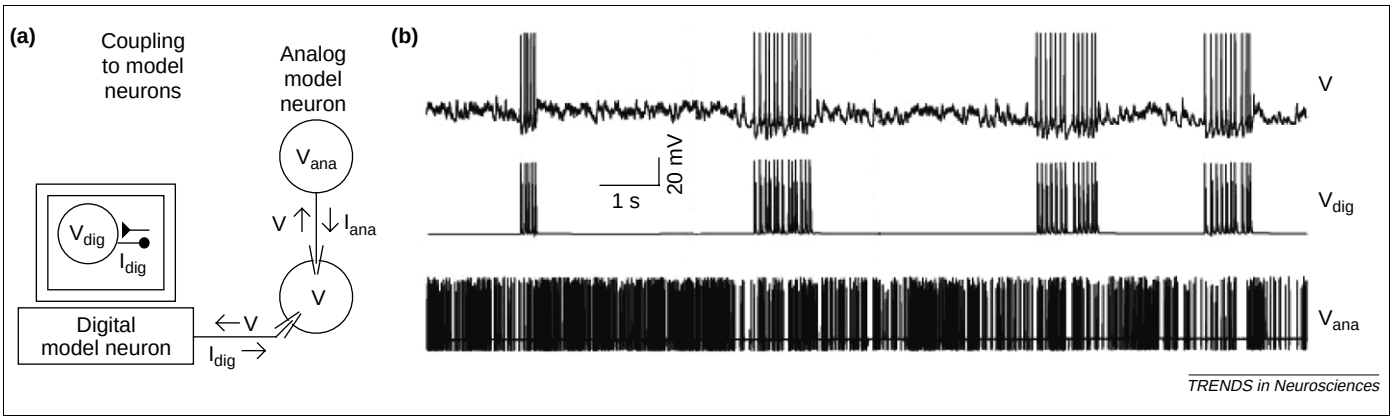

Figure 4. Building hybrid circuits of real and model neurons. **(a)** Schematic of the experimental configuration. The computer integrates the differential equations that describe the digital model neuron (dig) and its synaptic connections, while the analog model (ana) is an electrical circuit that mimics another neuron and its synapses. **(b)** Voltage traces from a thalamocortical cell (V), an analog retinal model neuron (V_{ana}) and a digital model reticular interneuron (V_{dig}). The thalamocortical neuron receives excitation from the analog and inhibition from the digital model neuron and excites the digital model neuron. The hybrid circuit generates spontaneous spindle activity similar to that in the sleep-like state. Adapted, with permission, from Ref. [13].

synapses. The anti-phasic oscillations exhibited by the two cells with artificial synapses are reminiscent of their behavior in the intact circuit, where they mutually inhibit each other through biological synapses. In an earlier study connecting two other stomatogastric ganglion neurons with reciprocal inhibitory connections, artificial synaptic connections allowed the examination of how the presence, frequency, and phase relations of oscillations depended on synaptic parameters and on intrinsic membrane conductances [30].

The approach of coupling two or more biological neurons with artificial inhibitory [6,30–33] or electrical [34–37] synapses has been used to study the effects of synapse strength [38] and dynamics on neuronal firing patterns [36], on the synchronization between oscillatory neurons [30,33,36,37] and rhythmic circuits [32], and on the intraburst firing pattern of bursting neurons [31].

Building hybrid computer–biological neural circuits

The dynamic clamp can provide an approach to the study of neural systems that falls midway between computer modeling and experimental electrophysiology. In modeling studies, we often want to assess the role of certain elements, such as individual conductances or synapses, that we might be able to model accurately. However, in a conventional modeling approach, we must incorporate these well-described elements into a model of a neuron or neural circuit that is inevitably much cruder. The dynamic clamp allows us to manipulate the well-modeled elements we wish to study with the same degree of precision and freedom that we have in a model, while allowing them to interact with real neurons or neural circuits, with all their complexities intact. Used properly, the dynamic clamp allows studies that combine the best features of computer modeling and experimental electrophysiology. An excellent example is the construction of hybrid circuits that involve interacting computer-modeled and biological elements (Figure 4a).

Figure 4b shows an example in which a real thalamocortical neuron was coupled using the dynamic clamp to two model neurons, one simulated by a digital computer and the other by an analog circuit [13]. The digital model neuron represented a reticular interneuron, while the analog circuit modeled a retinal ganglion cell. When coupled together, these three elements formed a circuit that could generate the type of spindle activity seen in the thalamus during sleep states. During sleep, the correlation between spikes in retinal ganglion cells and spikes in thalamocortical neurons is low, so that the cortex is functionally disconnected from its sensory drive. Systematic variation of the artificial inhibitory synapse from the model reticular interneuron to the biological thalamocortical neuron showed that the strength of this connection regulates the temporal correlation between the sensory input and the thalamocortical cell firing pattern [13].

Similar hybrid network configurations have been used to determine the effect of synaptic depression on oscillation frequency and bistability in reciprocally inhibitory pairs of neurons [7,39], to probe aspects of pain processing in the spinal cord [40], and to examine the effect of electrical coupling strength on synchronization of rabbit sinoatrial node cells [41].

Simulating in vivo *conditions*

Neurons and neural circuits are frequently studied in slice preparations. Slice preparations have distinct advantages in terms of accessibility for visualization and recording, but the disadvantage of being relatively silent. Because each neuron receives much less ongoing synaptic input in the slice than it would in an intact brain, neurons in slices are studied in an environment that is significantly different from that in which they normally operate. The dynamic clamp offers a way of studying neurons in slices while simulating *in vivo* synaptic input.

Figure 5a shows a dynamic clamp setup used to simulate *in vivo*-like synaptic input, both excitatory and inhibitory, entering a cortical pyramidal neuron [14]. In the absence of this input, the neuron fired regularly in response to current injection (Figure 5b, top), but when the simulated synaptic bombardment was introduced, the response was irregular with large subthreshold voltage fluctuations, as seen *in vivo* (Figure 5b, bottom). Figure 5c

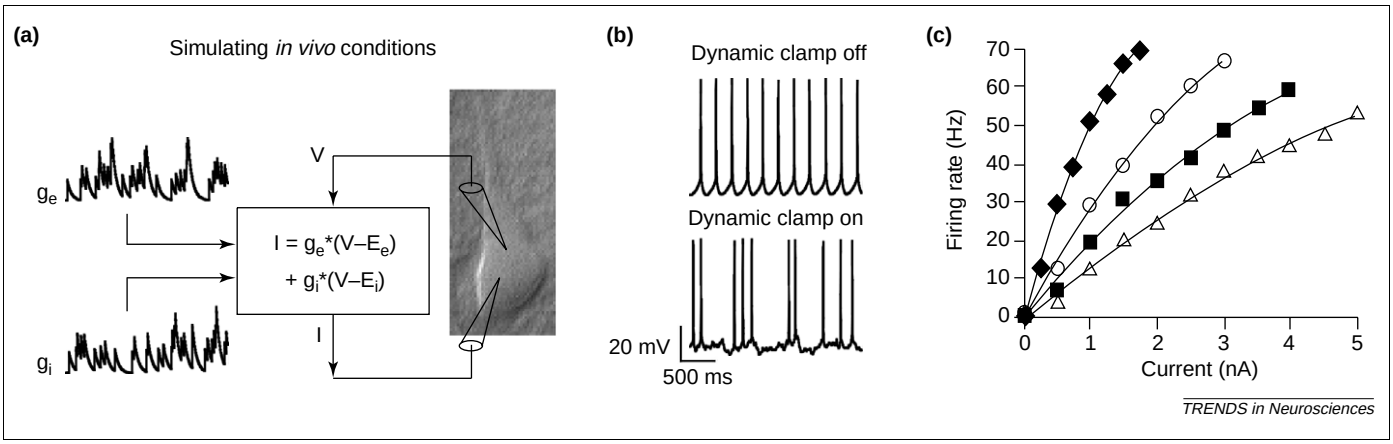

Figure 5. Simulating *in vivo* conditions in a slice preparation. **(a)** Schematic of the experimental configuration used to simulate balanced excitatory and inhibitory synaptic background conductances in a pyramidal neuron from a slice of rat somatosensory cortex. The dynamic clamp computes the total synaptic current produced by a stochastic model of ongoing cortical activity. The total synaptic current is the product of *in vivo*-like conductances g_e and g_i and the appropriate driving forces for excitatory (e) and inhibitory (i) synapses. **(b)** Voltage traces from a pyramidal neuron in response to constant driving current without (top) and with (bottom) artificial background synaptic input. **(c)** Firing rates of a neuron as a function of constant driving current without simulated background synaptic input (diamonds), with a given amount of background synaptic input (circles), with twice that amount (squares) and with three times that amount (triangles). Changing the level of synaptic background input modulates the gain of the neuron. Reproduced, with permission, from Ref. [14].

indicates that modulation of this synaptic bombardment can have important functional consequences. The slopes of the firing-rate versus input current curves shown in this figure decrease for increasing amounts of total dynamic-clamp simulated background synaptic input. This suggests that background synaptic input *in vivo* can act as a gain control mechanism [14,42,43]. The results of Figure 5c depend on the conductance modification that is due to the simulated synaptic input, so they could not have been obtained on the basis of current injection without using the dynamic clamp.

The dynamic clamp has been used to mimic realistic synaptic input patterns in many different neural systems, including auditory brainstem [44], lateral geniculate nucleus [45], basal ganglia [46], cerebellum [43,47–49], cortex [14,50,51], and avian nucleus laminaris [52]. In these systems, the technique has provided insights about the role of timing [47,48], rate [46], and synchrony [50,52] of synaptic inputs in postsynaptic signal processing.

Limitations of the dynamic clamp

A major limitation of the dynamic clamp is that the conductances it simulates are restricted to the site of current injection. As a result, conductances located far from the injection site can be mimicked only approximately. Normally, the injection site is the soma, but the advent of dendritic patch recording makes it feasible to simulate and apply conductances to dendrites. It would be particularly interesting to compare the effects of dynamic-clamp simulations carried out using dendritic and somatic injection sites. An alternative approach, which is useful for simulating dendritic conductances with somatic current injection, is to modify the current being injected by the dynamic clamp to include dendritic cable effects on the basis of a multi-compartment model.

Another limitation is that the dynamic clamp duplicates the electrical but not the signal conduction consequences elicited by specific ionic currents. In particular, with conventional electrode solutions, the dynamic clamp can simulate the electrical current from a set of Ca^{2+} channels, but it does not reproduce the changes in intracellular Ca^{2+} concentration that normally accompany the gating of such channels. In some cases, this limitation can be exploited to isolate voltage-mediated effects from other mechanisms.

Finally, the dynamic clamp shares a limitation with traditional current- and voltage-clamp techniques: artifacts of electrode resistance and capacitance. These artifacts can be minimized by using low-resistance electrodes, by using separate electrodes for voltage recording and current injection, or by temporally separating recording and injection through a single electrode using the discontinuous current-clamp technique.

Concluding remarks

To understand how neurons and neural circuits work, we must do more than simply watch them in action. We must probe and perturb them in various ways and study how they respond. Current clamping is one method for probing neuronal dynamics, and voltage clamping to realistic waveforms can provide interesting insights into the currents flowing during neuronal activity. The dynamic clamp, which creates a programmable conductance, provides yet another probe – one that permits a sophisticated range of perturbations. Dynamic-clamp experiments allow simulations with biological neurons or the creation of hybrid circuits of biological and model neurons. The dynamic clamp breaks down barriers between mathematical modeling and experimental electrophysiology by allowing theorists to model 'in the dish' and experimentalists to perturb their system in ways that, perhaps, only a modeler would imagine. It is our hope that use of the method will continue to expand as new and clever applications are devised, and that these applications will continue to reveal new aspects and marvels of neural circuit dynamics.

Acknowledgements

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