

Biophysically detailed modelling of microcircuits and beyond

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Definition: In this series of reviews, we will use the term microcircuit to denote a minimal number of interacting neurones that can collectively produce a functional output such as locomotor CPGs, the hippocampal circuits producing gamma and theta rhythm, and circuits in neocortex and cerebellum.

Abstract

Realistic bottom-up modelling has been seminal to understand which properties of microcircuits control their dynamical behaviour, like the locomotor rhythms generated by central pattern generators. We review recent modelling work on the leech heartbeat and the lamprey swimming pattern generators as illustration. Top-down mathematical modelling also plays an important role in analyzing microcircuit properties but it has not always been easy to reconcile results from the two modelling approaches. Most realistic microcircuit models are fairly simple and need to be made more detailed to represent complex processes better. We review methods to add neuromechanical feedback, biochemical pathways or full dendritic morphologies to microcircuit models. Finally we consider the advantages and challenges of full-scale simulation of networks of microcircuits.

Quantitative computational modelling is becoming an important tool in neuroscience research. Models at all levels are developed and studied, from the molecular processes underlying cellular and synaptic properties to brain-scale neuronal networks. Two complementary modelling strategies are used. “Bottom-up” simulations start from biophysically realistic models that mimic a lot of detail of the system under study and allow an open ended investigation of its properties. “Top-down” approaches use abstract models or pure mathematics to cast general principles of the system under study into a

minimal model, fully describing its essential properties with as few parameters as possible.

The central role of modelling is to promote synthesis of experimental data from different sources into a coherent picture of the system under study. The resulting model can then, for instance, demonstrate how seemingly unexplained phenomena are, in fact, a consequence of what is already known. Exploration of the model helps to identify truly unexpected findings, which then provide important input for the planning of new experiments. In this manner, modelling enables us to extract maximal knowledge from existing data and to find the most promising way ahead.

Bottom-up models have been quite successful in simulating microcircuits^[1-3] and we first review recent progress made using this approach to simulate the behaviour of two central pattern generators (CPGs), in the leech and the lamprey. Such models traditionally consist of small networks of synaptically connected ‘point neurones’, i.e. models without morphology. The active conductances responsible for the excitable properties of the neurones and the synaptic conductances are simulated in a physiologically realistic manner^[4]. Mathematical approaches used in top-down modelling have also contributed to better understanding of the two CPGs, but the two modelling approaches have not always produced congruent results. Such differences can only be resolved by intensive interactions between the modellers and experimentalists involved. Some authors have advocated combining bottom-up and top-down models for the same system^[5], but these techniques are not yet widely used.

In the second part of this review we consider how one can make the simple network models more elaborate so as to increase their realism. We describe simulating neuromechanical feedback, adding biochemical networks involved in synaptic learning, the incorporation of realistic neurone morphology and increasing the size of the network to full-scale (all neurones modelled). This part uses examples from simulations of the other microcircuits reviewed in this special issue ^[1].

Modelling the leech central pattern generator

Because one can identify individual invertebrate neurones and because their cellular properties and connectivity are stereotypical it may, in principle, be possible to create complete models of invertebrate CPGs, replicating all important properties. A system where much progress has been made is the circuit responsible for generating the heartbeat rhythm in the medicinal leech. The sub-circuit of heart interneurones (HN neurones) in the first 4 ganglia (Fig. 1b) inhibits segmental motoneurones to control the rhythmic constrictions (1 Hz) of the bilateral heart tubes. The primary foci of oscillation of the CPG are the pairs of HN neurones in ganglia 3 and 4 where HN neurones inhibit their contralateral partner. This reciprocal inhibition makes the unstable intrinsic bursting properties of HN neurones more robust ^[6] and alternating, resulting in a half-centre oscillator behaviour (Fig. 1a). A first series of models ^[7-9] investigated the interaction between the synaptic inhibition, which is both graded and spike-evoked, and the voltage-gated currents in one pair of neurones as this forms an elemental oscillator. An important and unexpected modelling prediction was that not only the hyperpolarization-activated h current but also slow Ca^{2+} currents, activated during the burst, have a strong effect on the period of oscillation (Fig. 1c). Of particular importance is how effectively the inhibitory

phase removes the inactivation of the Ca^{2+} channels, as this will determine their capacity for activation during the burst phase and the amount of inhibition that can be generated. This prediction was experimentally confirmed when realistic waveforms were used to voltage clamp HN neurones^[10] which led to further improvements of the model^[8].

The pairs of HN neurones in ganglia 1 and 2 link the oscillators in ganglia 3 and 4 through inhibitory synapses (Fig 1b) and are therefore called coordinating interneurones. Their role was investigated in more recent models^[11, 12]. The bottom-up approach, using previously developed models as building blocks to create larger network models, worked in this case as a fairly realistic 6 neurone segmental circuit could be produced by adding simple models of 4 coordinating interneurones to one elemental oscillator circuit. Spike mediated inhibition from coordinating interneurones increased the oscillation period but the oscillation behaviour did not change qualitatively^[11].

When this model was expanded to the full 8 neurone circuit (Fig. 1b) it could replicate the phase relationships between HN3 and HN4 neurones when they spontaneously entrain each other under “natural” conditions (closed loop)^[11] but not when the CPG was driven by current injection in one neurone (open loop)^[13]. This problem was solved with a more detailed model^[12], which explored whether the phase differences are due to an asymmetry in synaptic coupling or to a difference in cellular excitability leading to different intrinsic oscillation frequencies of the elemental oscillators. A similar question dominated the lamprey CPG field for a long time (see further). The bottom-up leech modelling^[12] demonstrates that both mechanisms can contribute, depending on the experimental condition. In the closed loop condition higher excitability of the HN3

neurones dominate while in the open loop condition the asymmetry of the circuit (HN3 neurones inhibit the coordinating neurones more, Fig. 1b) determines the behaviour.

More recently the leech CPG has also been the subject of extensive top-down mathematical analysis which investigated in more detail the transition from tonic to bursting spiking in isolated neurones ^[14] (Fig. 1e-h) as was observed in earlier experimental studies ^[6]. The approach used was to reduce the complexity of the HN model by blocking or ignoring several active conductances so that it could be reduced to 3 variables, with one differential equation for each. Bifurcation theory ^[15] (Fig. 1g) allowed the authors to show that a single variable, the half-inactivation of a persistent K^+ current, controls the distance between the attraction domains for tonic spiking and for bursting (Fig. 1e). Again these predictions are amenable to experimental study.

Modelling the lamprey spinal pattern generator

The lamprey spinal locomotor system ^[1, 16] generates a wave of neural activity along the body during swimming, normally travelling in the head to tail direction but reversed during occasions of backward swimming. It comprises two main types of premotor interneurons, in addition to the motoneurons driving the swimming muscles. These are the ipsilaterally projecting excitatory glutamatergic interneurons and the contralaterally projecting glycinergic inhibitory interneurons (see ref. 1 in this issue for a circuit diagram). The burst-generating network is extended in the rostro-caudal direction such that the excitatory interneurons project a few segments rostrally and caudally whereas the crossed inhibitory interneurons may extend up to twenty segments caudally. This connectivity is responsible for intersegmental coordination and the propagation of the

locomotor activity wave along the body. The crossed inhibition is mainly responsible for the left-right alternation of locomotor activity.

Many aspects of the lamprey CPG have been studied with biophysically detailed modelling, including segmental burst generating mechanisms ^[17, 18], steering ^[19] and plasticity ^[20]. Recently, a fundamental shift in our understanding of this system has occurred. It started with early modelling results using top-down connectionist models of recurrent excitatory networks. This demonstrated that a network of mutually exciting and adapting interneurons by itself (Fig. 2c), in the absence of any inhibition, would be capable of rhythm generation in the locomotor frequency range ^[21]. This hypothesis was subsequently elaborated by simulating biophysically more detailed models ^[18]. The predictions were recently confirmed with intricate experiments which involved a longitudinal transection of the lamprey spinal cord (Fig. 2a-b) ^[22, 23]. These findings challenge the traditional view of vertebrate locomotor rhythm generation as based on half-centre oscillators in which reciprocal inhibition is necessary for oscillations to occur (e.g. Fig. 1b).

The intersegmental coordination during locomotion has also been modelled extensively. The lamprey maintains approximately one wavelength of curvature along its body when swimming, independent of swimming speed ^[16]. Thus, the lag between burst onsets in consecutive segments constitutes a constant fraction of the cycle duration (referred to as a constant phase lag) independent of cycle duration, at least in the intact animal. Intersegmental coordination is also flexible; *in vitro* experiments have demonstrated that an isolated piece of spinal cord can be stimulated selectively such that it displays a coordination corresponding to either forward or backward swimming ^[24].

The properties of the microcircuitry responsible for the constant phase lag have been the topic of extensive discussion between bottom-up and top-down modellers. Bottom-up models and experiments based on studying the effect of excitatory glutamate agonists on network bursting frequency ^[16, 24] suggested that the principal mechanism behind the intersegmental phase lag was the higher excitability in rostral segments ^[16]. Top-down approaches, on the other hand, pointed towards asymmetric synaptic coupling ^[25, 26], since the models using chains of coupled oscillators ^[26] better mimicked the behaviour of the spinal cord under conditions of mechanically forced oscillations ^[27].

Similar to our discussion of the leech intersegmental coordination ^[12], these divergent views partly emerged from experiments of a quite different nature that seemingly favoured one model over an other. A current challenge is to unify the different theories and models such that progress can be made towards a more coherent view.

As described above the underlying synaptic coupling is asymmetric, but its short-range components appear more important for effective intersegmental coordination as demonstrated by abstract ^[28] and more detailed computational models ^[17]. In order to further elucidate the cellular and synaptic mechanisms behind intersegmental coordination, a biophysically detailed full-scale model of a reduced experimental preparation, the lamprey hemi-spinal cord, is currently being simulated (Fig. 2d-e).

Incorporating neuromechanical models

The lamprey CPG is influenced by sensory feedback from the generated body undulations ^[16]. Can such interactions also be incorporated into the neuronal circuit

models? More generally, can a model of a spinal pattern generator be connected to models of muscles and limbs to capture the entire movement generation process?

As all neural circuits have evolved in order to function in specific natural environments, any study, being in vitro or a simulation, ignoring the mechanical context may be severely limited. For example, the function of the leg control circuits in the stick insect thoracic ganglia is critically dependent on feedback from a whole set of mechanosensors signalling joint positions, velocities, strain, etc. ^[29]. From this perspective, the central goal is to realistically replicate the feedback received via mechanosensors while other aspects of the movement produced is secondary.

Incorporating mechanical components into a simulation is not trivial. The mathematical models required for simulating body movements are quite different from the ones used when modelling neural activity and signalling. The interface between neurones and mechanical behaviour, i.e. muscles and mechanosensors, must therefore be described by models compatible with both mathematical languages. For mammals, muscle models available in the literature can serve this task ^[30], while insects and lower vertebrates may require more research in order to come up with sufficiently accurate models. On the sensory side the main obstacle is to find the transfer functions that relate mechanical action to the neural signal. When accurate feedback signals are not crucial, simple linear transfer functions may suffice; otherwise each variety of mechanosensor will require a specific model equation.

In a study of neuromechanical interaction in lamprey swimming ^[31] both muscles and mechanosensors were modelled as linear. The gross simplifications made when

describing body mechanics, interaction with surrounding water, etc. made it irrelevant to incorporate more subtle models. Similar approaches have been successful in simulating both the swimming and walking behaviour of the salamander ^[32]. In studies of walking in cats more accurate models of muscles and sensors have proven important in mimicking natural behaviour ^[33].

Interaction with subcellular modelling

Intracellular signalling cascades can change microcircuit computations by modifying the intrinsic properties of neurones or the strengths of synaptic connections. They are important in the homeostatic control of these properties ^[34], but as the signalling processes involved are at present poorly understood no detailed biophysical models exist. In the future such models will have to bridge the gap in timescales between electrical neuronal activity (milliseconds to minutes) and homeostasis (days). Fortunately, solutions are being developed for multi-timescale modelling ^[5, 35].

Signalling pathways can be activated by synaptic input and there is a rapid growth of models simulating this interaction. Some studies focus on information processing by biochemical pathways, like temporal computation ^[36, 37], but most simulate the induction of synaptic plasticity in hippocampus or cerebellum. We review recent work on the latter.

Classical conditioning of the eyeblink response is a form of associative learning that involves the induction of long-term depression (LTD) of parallel fibre (PF) synapses onto cerebellar Purkinje cells ^[38]. LTD is induced by a raise of postsynaptic Ca^{2+} concentration, caused by PF evoked Ca^{2+} release from stores. It is assumed that this release is potentiated by voltage-gated Ca^{2+} influx activated by preceding climbing fibre

input ^[39]. Several models simulating the complex intracellular signalling cascades involved have explored whether this mechanism is sufficient for acquisition of learning ^[40-42]. These models confirmed that the kinetics of biochemical interactions leading to Ca^{2+} evoked PKC activation ^[38] may explain the temporal sensitivity during the learning phase ^[41]. But they also indicated that additional mechanisms, like a MAP-kinase dependent positive feedback loop may be involved ^[42], which was recently experimentally confirmed ^[43]. Furthermore, these models explored the effects of other sources of Ca^{2+} influx ^[40], like the non-associative PF-induced voltage-gated influx ^[44] that may interfere with learning ^[45]. Finally, at the microcircuit level, they allow for a quantitative comparison between models which make biochemical mechanisms responsible for learning the timing delay of the conditioned response ^[46] to models which put this learning at the network level ^[47].

Interaction with cellular modelling

Most microcircuit models consist of networks of point neurones ^[1-3]. But as dendritic integration of synaptic input ^[48] can have a strong effect on a neurone's input-output function there is a growing interest in incorporating morphologically realistic models of neurones in microcircuit models. The standard technology for modelling dendrites is compartmental modelling with active conductances ^[4] but using this in microcircuit models introduces several challenges.

First, several models may need to be created, each requiring 10s-100s of poorly constrained parameters. In the past these parameters have often been laboriously hand-tuned ^[49] but advances in optimization technologies make automatic parameter searches

an attractive alternative. In general, evolutionary strategies ^[50], which are better suited for real-number parameters than genetic algorithms, outperform other methods in high dimensional problems ^[51] and give better results in the presence of noise ^[52], two important issues in neural modelling. An additional advantage of these methods is that they produce multiple possible solutions which corresponds to the large variability found in real neurones ^[53, 54].

This brings us to the second challenge: variability of neuronal morphology. In network modelling it is well known that the introduction of heterogeneity of neurone models can cause new dynamic modes to appear ^[55] and such networks are often more robust to noise than homogeneous ones ^[56, 57]. In networks using simple neurone models heterogeneity can be introduced as variability of the leak current or of voltage-gated channel densities. When more detailed models are used one also has to consider variability in neuronal morphology. Unfortunately, for most neurones, only a few reconstructed morphologies are available and it requires much work ^[58] to add more samples. Nevertheless this approach, taken by the Blue Brain project which plans to create a morphological realistic model of a complete cortical column (<http://bluebrainproject.epfl.ch/>), may be preferred over aggregating reconstructions from many different laboratories. Several recent modelling studies showed that inter-laboratory differences in experimental methods cause so much divergence in neuronal reconstruction that, functionally, this could be data from different neurones (Fig. 3) ^[59, 60]. Instead of using real reconstructions one can also generate ^[61] or grow ^[62] random dendritic morphologies based on accurate statistical descriptions of the dendrites modelled. While this may be ultimately the most rewarding approach, it has not yet been evaluated in realistic microcircuit simulations.

The final problem is synaptic wiring. To understand the morphological distribution of connections one has to reconstruct the axons of stained neurones as well. In some cases, for example invertebrate neurones where the spike initiation sites are in the axon (Fig. 1b), one may have to model the axons completely. Fortunately, in most microcircuit models delay lines^[57, 63] can be used, where only the time of arrival of a spike at each synapse is computed without simulating spike propagation. Connecting the neurones requires custom code for each type of axon modelled^[64], as no general models specifying connectivity rules at the morphological scale exist. Additionally, currents generated by single synaptic contacts have to be simulated instead of compound synaptic currents, as is done in most microcircuit models. In the simplest case this requires adapting the synaptic conductances used^[64, 65]. Regrettably, most microcircuit models are sub-sampled networks, i.e. not all neurones are represented and substantial synaptic input is lacking. In single neurone models one can compensate for absent presynaptic neurones by manipulating firing frequencies of input lines^[66] but in microcircuits one can only increase the available synaptic conductances. When using real morphologies this is limited by the possible saturation of synaptic currents because of the high local input impedance of small dendritic branches and spines. Therefore the best, but also computationally most demanding, approach may be to go for full-scale modelling (see next) where all presynaptic neurones in the microcircuit are represented.

Interaction with large-scale network modelling

A microcircuit is, by definition, a component of a much larger network. It can be simulated to some degree in isolation, especially when it can be related to a reduced *in*

vitro preparation, e.g. a piece of lamprey spinal cord. But more often it is in reality embedded in a mosaic of similar modules which requires large-scale network modelling. A major benefit of a large-scale model is that by providing a realistic number of presynaptic inputs it removes the need to increase synaptic connection probabilities or conductances ^[63]. Such compensations tend to distort significantly the dynamics of the network.

Fortunately, one reason for avoiding large-scale simulations is gradually disappearing. Although the reduction of dimensions and increase of clock frequencies of integrated circuits may be approaching their limits, the number of processors operating in parallel in next generation computers will increase dramatically. Since neuronal networks represent quite homogenous computational structures, parallel simulation is relatively straightforward ^[67, 68]. Thus, in the near future, computer power may no longer prevent us from putting together and study large and even full-scale models of global brain networks.

Of course the number of under-constrained parameters increases when going from a small to a much larger network model. Currently parallel simulation of networks of millions of neurones and billions of synapses can be performed on large cluster computers. Such models include several billion parameters. Fortunately, neuronal networks are typically described as comprising a limited number of cell types, with basically the same properties but some variation within the population. The parameter used for one neurone of a certain type can be used for the others as well, possibly with a compact description of a distribution around a mean (Fig. 3e). This holds also for the synaptic interactions. Moreover, synaptic conductances are not determined arbitrarily but

are the result of genetic specification interacting with plasticity and learning rules which couple them to historical network activity ^[69]. In practice, the number of truly free parameters is therefore more or less independent of the actual number of neurones and synapses used to instantiate the network.

Further, somewhat unintuitive, for really large networks there is little extra cost to simulating complex neurone models. Contrary to the case for single neurones and small networks, the solution methods used for dendritic integration ^[70] do not add significantly to simulation time, since synaptic computation dominates because of the large number of contacts modelled. Fortunately, the spiking communication between neurons often does not require fast inter-processor communication, which can be a problem in parallel cluster computing. As long as neurons only interact with spiking events over delay lines Address Event Representation based communication can be used ^[67] and parallel neural simulation is bound by local computation. As soon as continuous cell-to-cell interactions, like electrotonic synapses or graded transmitter release (Fig. 1), needs to be simulated, parallel simulations have to be organized quite differently and the communication overheads become potentially performance limiting.

Concluding remarks

Quantitative computational modelling has come to neuroscience to stay. As these techniques are becoming increasingly integrated with experimental research, there will be more knowledge extracted from existing experimental data and model predictions will enter more routinely into the planning of new experiments. But to succeed a better

integration between bottom-up modelling, which will rapidly increase in detail because of affordable massively parallel computers, and top-down approaches is needed.

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Figure Legends

Figure 1. Two different approaches to modelling the leech heartbeat CPG. On the left-hand side (a-d), the models try to reproduce the experimental data as much as possible [7-9]. Afterwards, the analysis of each parameter's influence gives a better understanding of the microcircuit dynamics and leads to new predictions. On the right-hand side (e-h), theoretical considerations applied to a simplified model of the HN neurone predict a particular behaviour of this neurone [14]. (a) Simultaneous intracellular recordings of the two HN interneurons in ganglion 4. This pair of reciprocally inhibiting neurones forms a half-centre oscillator. (b) Schematic showing how the coordinating neurons from ganglia 1 and 2 inhibit the half-centre oscillators in ganglia 3 and 4; the coordinating neurons initiate spikes in their axons in ganglia 3 and 4. Note that HN3 inhibits the coordinating neurones in both ganglia 3 and 4 while HN4 does so only in ganglion 4. (c) 4th-generation model of the segmental half-centre oscillator [8]. Presynaptic low-threshold Ca^{2+} current (upper trace) in HN(L) progressively declines during burst leading to decreased inhibition of the HN(R) neuron. At the same time the amplitude of the hyperpolarization-activated h-current increases in the HN(R) cell (lower trace). These two phenomena lead to a rebound bursting of the HN(R) neuron which then inhibits the HN(L) cell. (d) Effect of varying the maximal conductances of the intrinsic persistent Na^+ current (g_p), the slow Ca^{2+} current (g_{cas}), and the hyperpolarization-activated current (g_h) on the period of the elemental oscillator model. (e) Bifurcation diagram of a slow-fast system of differential equations. The abscissa represents the slow phase space variables while the ordinate follows the fast ones. In this singularly perturbed system, the intersection of nullclines gives two periodic orbits: one stable (LN) and one

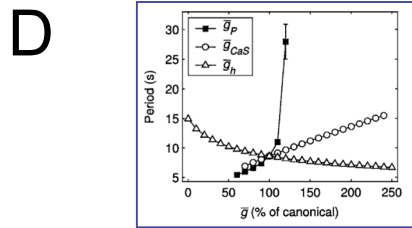
saddle (LS). (f) Under the assumption of blockade of Ca^{2+} currents and partial blockade of outward currents, and ignoring persistent Na^+ current, the HN interneurone can be modelled with two currents only: a fast Na^+ (I_{Na}) and a persistent K^+ ($I_{\text{K}2}$). The remaining variables are the membrane potential (V), the activation of $I_{\text{K}2}$ ($m_{\text{K}2}$) and the inactivation of I_{Na} (h_{Na}). The bifurcation diagram is drawn in the $(m_{\text{K}2}, V)$ plane. (g) Coexistence of spiking (red) and bursting (blue) modes in the model, shown in the $(m_{\text{K}2}, V)$ plane (top diagram) and with voltage traces obtained from slightly different initial conditions (bottom lines). (h) For particular values of $V_{\text{K}2\text{shift}}$, the shift of membrane potential of half-inactivation of $I_{\text{K}2}$ from its canonical value, chaotic bursting (top trace) and smooth transitions between bursting and spiking (bottom) can be observed. Modified with permission from [8, 12, 14]

Figure 2. Large-scale CPG simulation of lamprey hemispinal cord. On the left-hand side (a-c) experimental data (reproduced with permission from [23]), on the right hand side results from a simulation of a full-scale model of the network of excitatory interneurons. The network comprises 3000 conductance based model neurones and more than 110.000 glutamatergic synapses. Activity during 3 seconds is shown. (a) Lamprey hemicord preparation rigged for electrical stimulation and recording of ventral roots (VR) activity with pipette electrodes. (b) A brief train of pulses delivered via the stimulating electrode (stim) evokes a long bout of motor bursting at the VRs. (c) Model network that accounts for the fast rhythmic bursting expressed by the hemicord, Only one hemisegment is shown, with the circles representing groups of neurons. Excitatory interneurones (E) form an interconnected network able to sustain repetitive firing by positive feedback, mediated by both fast ionotropic and slow metabotropic synaptic transmission. Fast synaptic

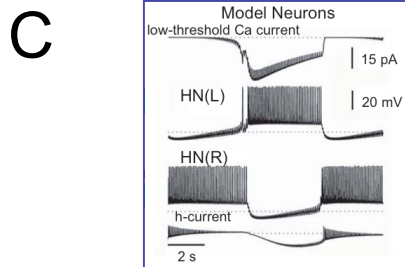
interactions promote a certain degree of synchronization across the population. Phasic excitation is relayed to the motoneurons (MN). At each cycle, the individual action potentials from many MNs converge in the VR, where a burst is recorded. (d) Spike raster plot of activity in all simulated neurones sorted rostro-caudally (ventral root (VR) 1 – 100). The overall bursting pattern as well as a 1% per segment phase lag can be seen. (e) Simulated average motoneurone membrane potential and ventral root EMG synthesized from the model output is shown for three different segments. The delay of onset of consecutive bursts is marked with dashed lines. (f) Simulated membrane potential of five different excitatory interneurons in one of the middle segments. Model parameters for neurones and synaptic connectivity have a significant random variability and therefore the activity of different neurones displays quite variable spike patterns.

Figure 3. Difference in properties of archived neuron reconstructions. The morphological properties of CA1 hippocampal pyramidal neurons measured on reconstructions obtained from 3 different internet archives (S_vivo and S_vitro: Duke/Southampton archive, HAS: Hungarian Academy of Sciences archive and UTSA: University of Texas at San Antonio archive, references in ^[60]). (a) Quantitative morphometric differences between cell groups shown as the relation between size of the cells (horizontal axis) and the average diameter of their dendrites. Each data point represents one cell and the population means ± 1 SD are shown. Modified with permission from ^[60]. (b) The large morphometric differences have functional consequences: right neurone attenuates synaptic current much more than left one. Simulated localization-dependent attenuation of IPSCs in a neuron from the UTSA

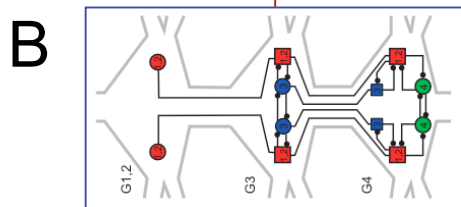
archive (left) and from the S_vitro group (right). Colours code the attenuation at the site of the synapse, which is computed as the ratio of maximum amplitude of synaptic current at this site over amplitude in the soma. Somata are not drawn and diameters of right cell are drawn at a 3 times larger scale than those of the left cell to enhance visibility.



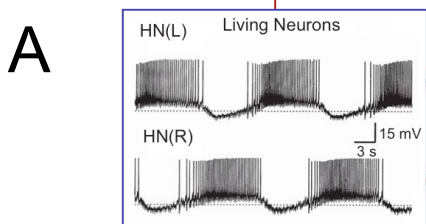
that reveals regulation of network activity by an intrinsic current



where the effects of I_{Ca} inactivation and I_h conductance on burst duration are analysed



allows detailed model construction

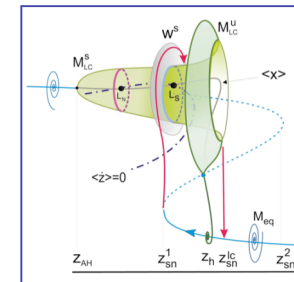


experimental data

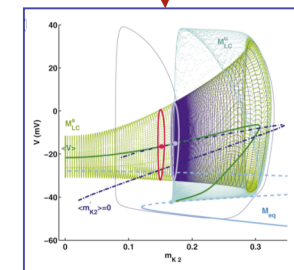
bottom-up approach

top-down approach

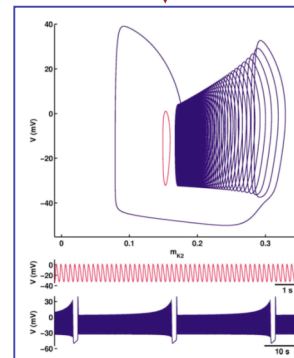
bifurcation theory of slow-fast systems



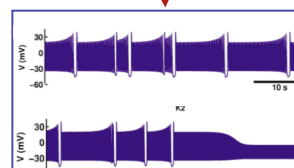
applied to a simplified model of the leech neuron

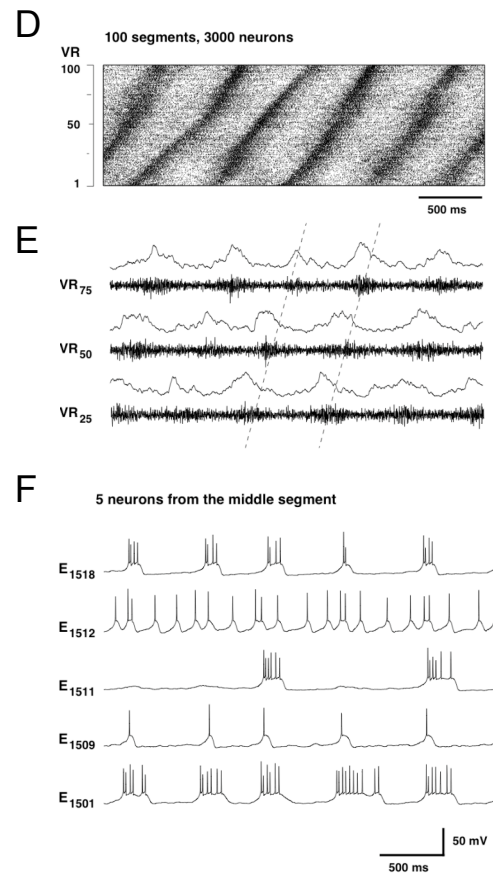
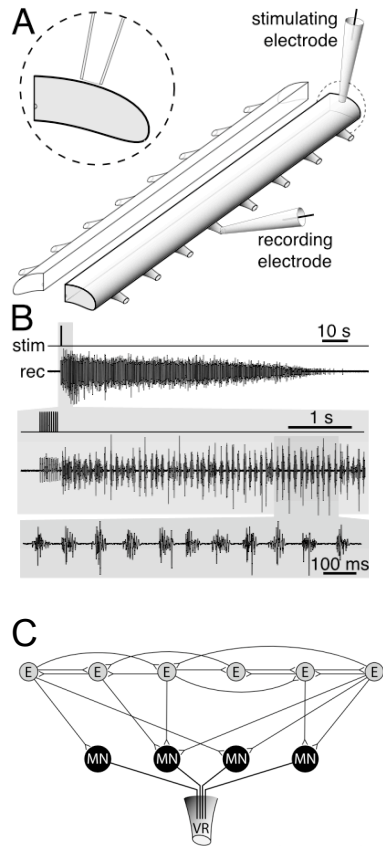


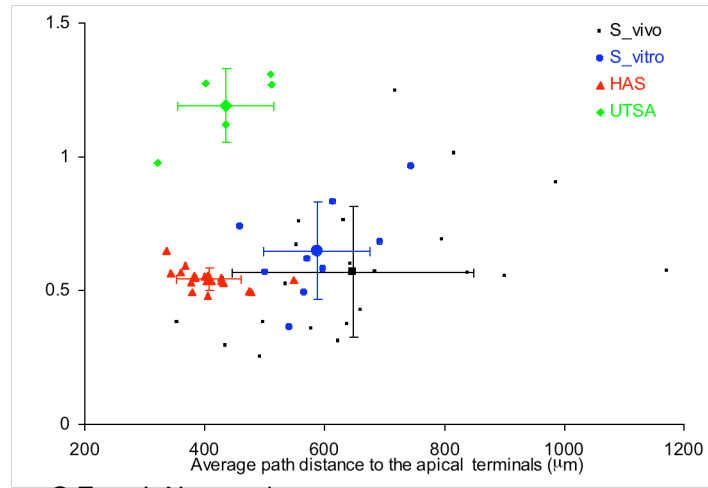
gives a description of its bistable behavior



and predicts chaotic bursting and smooth transition to spiking





A

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B