A large scale model of the cerebellar cortex using PGENESIS [1]

F.W. Howell [a] J. Dyhrfjeld-Johnsen [b] R. Maex [b] N. Goddard [a]
E. De Schutter [b]

[a] *Institute for Adaptive and Neural Computation, Division of Informatics, University of Edinburgh, 5 Forrest Hill, Edinburgh EH1 2QL, Scotland*

[b] *Theoretical Neurobiology, Born-Bunge Foundation, University of Antwerp, Universteitsplein 1, 2610 Wilrijk, Belgium*

Abstract

In an investigation into the transformation of mossy fiber input to Purkinje cell output in the cerebellar cortex, we have developed a network model including a sophisticated compartmental model of the Purkinje cell. Analysis and simulations demonstrated the need to include a large number of parallel fibers (244,000) to obtain realistic Purkinje cell firing patterns for random mossy fiber input. Using smaller numbers of parallel fiber inputs resulted in unrealistic Purkinje cell spiking characterized by spontaneous dendritic calcium spikes. Because the scale required is beyond workstation capabilites, we used a 128-processor Cray T3E running PGENESIS. This size network could produce realistic spiking patterns provided the stellate cell inhibition was tuned carefully.

Key words: Large scale modelling; PGENESIS; Cerebellum

1 Introduction

The structure of the cerebellar cortex circuit is well known but the precise computation it performs is still unclear [5]. The cerebellar cortex is distinguished by a very regular anatomy [9], which lends itself very well to grid-based modelling, but also by very long axons (the parallel fibers can be up to 5 mm long [13]). We aimed to investigate the behaviour of this circuit from mossy fiber input to Purkinje cell output, by modelling the network of granule, Golgi and stellate cells in a 6mm slice of a rat's cerebellum.

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2 Model of the cerebellar cortex

The model was constructed using the GENESIS simulation tool; single compartment models were used for all cells except for the Purkinje cell, for which a large 4,500-compartment model based on the real morphology was used [3,2]. The granular layer was modelled as before [11,12] and models of individual neurons were based on available experimental data. Synaptic weights onto the Purkinje and stellate cells were based on experimental data for single contacts. The basket cells, and climbing fiber input were not modelled. The model consisted of a 2D mesh of mossy fibers providing random spike input to a grid of Golgi cells and granule cells. The granule cells were positioned in 3D space and the shape of the parallel fiber axon was used to establish synaptic connections to Golgi cells and Purkinje cell spines within range. The ascending granule cell axon input to Purkinje cells was included [7]. A cloud of inhibitory stellate cells was modelled around each Purkinje dendritic tree, and the connnections from parallel fiber to stellate, and from stellate to Purkinje cells were made. The granular layer network synapses were tuned to minimize synchronization of its activity [12]. The model was in the first instance tuned to generate realistic in vivo simple spiking behaviour of the Purkinje cell. Previous work has shown that this requires a balance of excitatory (parallel fiber) and inhibitory (stellate cell) input to the Purkinje cell [10]. Initial simulations showed that realistic spiking patterns could not be obtained with a network size including 22,000 granule cells [4]. The limited number of parallel fiber contacts possible in such a setup did not generate enough synaptic current onto the Purkinje cell dendritic tree to prevent the generation of spontanous dendritic calcium spikes which normally are absent in vivo [10].

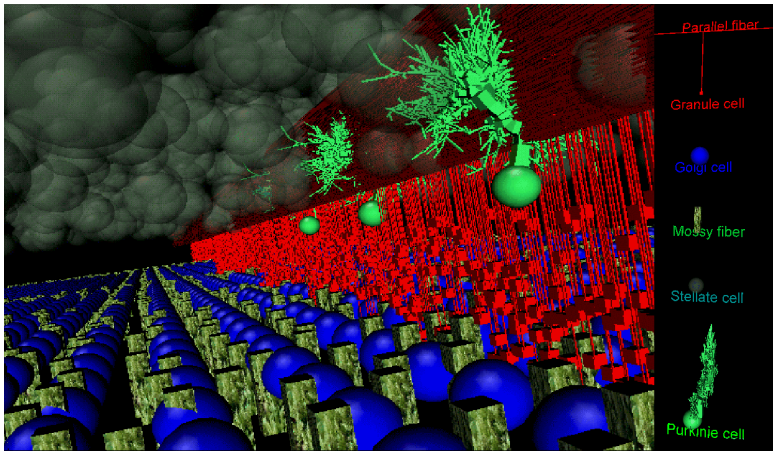

Fig. 1. A view from inside the model , with a single slice of granule cells (1% of the total).

3 Simulation scale

A single rat Purkinje cell can receive up to 200,000 synaptic inputs [8], and modelling 200,000 compartment-based cells (each of which contains a number of channels) involves large amounts of compute time and memory. The largest network which would run on a workstation with 1GByte of memory had 60,000 granule cells, 300 mossy fibers, 300 Golgi cells, 300 stellate cells, and one Purkinje cell, and took 44 hours to simulate 2.0 seconds of behaviour, with a 20 usec timestep. The scale of the GENESIS model was limited by memory. Because of this, and the difficulty of doing parameter searches when it takes two days for each simulation run, a version for parallel machines was developed using PGENESIS, the parallel version of GENESIS.

4 PGENESIS

PGENESIS is an extension to GENESIS which runs on a large range of parallel computers and networked workstations [6]. It is especially appropriate for network models and parameter searches, where there is relatively little communication between components of the simulation (cells or simulation runs, respectively) compared with the communication between compartments in a single-cell model. While it does not automatically partition the simulation model across a parallel computer or workstation network, it allows the modeller to specify the partition and to create synapses between cells on different processors, and it does automatically synchronise the components running on different processors to ensure correct simulation behaviour. To aid the modeller in creating an efficient partition of the network model, PGENESIS provides diagnostics indicating what percentage of processor time is spent in various tasks including simulation, synchronisation and data communication. The most efficient partition is the one which maximises the percentage of processor time spent on simulation.

In order to work out a reasonable partition, the diagnostic facilities of PGENESIS were used to determine that the computation time to simulate each Purkinje cell was approximately 1000 times greater than the time to simulate each (simpler) granule cell, and that the other single cells were of the same order of complexity as the granule cells. A reasonable load balance therefore would be one Purkinje cell on one processor, and 1000 granule cells per processor on all the others. The initial partition chosen allocated a Purkinje cell to a processor, and sliced the rest of network along the axis of the parallel fibers, giving an equal number of cells to each processor. This partition led to a communications imbalance, as the slices of Golgi cells near to the parallel fibers received the bulk of granule cell synaptic input, and those processors proved

the bottleneck. This was resolved by slicing the network perpendicular to the parallel fiber axis, which resulted in an even communication balance. The final parallel model required 128 processors. 16 processors simulated one Purkinje cell each. The 244,000 granule cells were spread between the remaining 112. Total run time for 2.0 seconds of simulated time was 2.5 hours, of which 1 hour was spent constructing the distributed model in processor memory. Figure 1 shows the slice of granule cells allocated to a single processor.

5 Results

Realistic firing patterns could be obtained only if at least 49,000 parallel fiber inputs to the Purkinje cell model were simulated. While it was possible to suppress the spontaneous dendritic calcium spikes at lower number of synapses (25,000), the dynamic range was very poor and the spiking pattern included an abundance of unrealistic doublets. Figure 2 shows the Purkinje model firing complex spikes when there are too few granule cells; figure 3 shows simple spikes obtained by increasing the number of parallel fibers. For the larger network sizes (49,000 parallel fiber inputs) we found, as was theoretically predicted [1], that the lack of feedback inhibition in the molecular layer made the Purkinje cell simple spike firing pattern very sensitive to the tuning of the physiological parameters which determine the feedforward inhibition. In particular, higher numbers of stellate cell synaptic contacts (2,300 or more) were needed than have been estimated based on indirect anatomical criteria [14]. The results were also very sensitive to the weight of parallel fiber to stellate cell synapses, indicating a critical dependence on the firing properties of these inhibitory neurons.

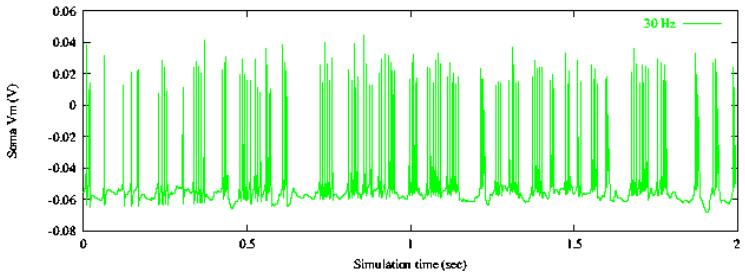

Fig. 2. This plot of Purkinje soma voltage against time shows unrealistic complex spikes, resulting from a model with 22,000 granule cells in response to 30Hz random mossy fiber input.

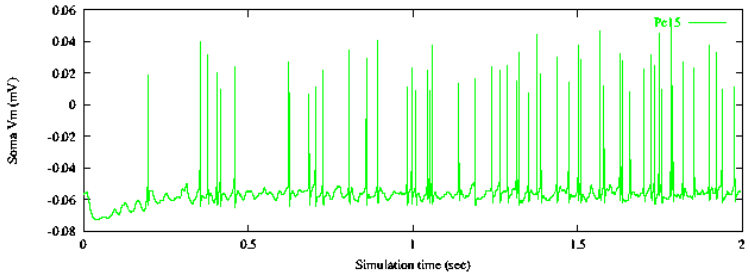

Fig. 3. Increasing the number of granule cells to 244,000 leads to simple spikes.

6 Discussion

We can draw two conclusions from the work reported here, one methodological and one scientific. First, as a simulation methodology, we have shown that it is possible to simulate very large network models using PGENESIS on an advanced parallel supercomputer. There have been very few neuronal network models which have used the degree of parallelism reported here, and none we are aware of that model at the compartmental level. While highly model dependent, the scaling results demonstrate that PGENESIS achieves close to linear speedup in simulation time over the range studied. We believe that substantial credit for this achievement must go to the extraordinarily good design of the Cray T3E interconnection network. We anticipate that similar speedups should be achievable on shared memory architectures, and are investigating the performance limits for network workstation clusters. The most interesting, and perhaps distressing, scientific conclusion is that there are neuronal systems, viz the cerebellum, for which radically scaled-down simulation models cannot achieve realistic behaviour. In this case we believe that a simulation at 10% of real scale was necessary because realistic Purkinje cell firing requires an appopriate large number of relatively weak synaptic inputs [10] which is only achieveable with very large numbers of afferent units. There is no reason to suppose this characteristic is limited to Purkinje cells.

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