topological dynamics, the best of which was prompted by happening to read Thurston and Weeks' Scientific American article on Three-manifolds. I was struck by the example they gave of a two-manifold, namely the configuration space of a triple linkage, which they showed has genus 3. I asked myself whether the free dynamics of the linkage might be Anosov and following numerics by a PhD student Tim Hunt in Cambridge, managed to prove this in a certain parameter regime. In Cambridge I was also invited to help steer a project on spatially extended dynamics. I tried out an idea I had for responding to Sinai and Bunimovich's challenge to make a coupled map lattice with non-unique phase on the group. One of the postdocs Guy Gielis explained to me some interesting stochastic systems that showed similar effects and I realised we could simulate them using coupled map lattices. This was probably my real entry into complex systems. Using the understanding gained, I proposed a mathematical formulation of the trendy concept of "emergence". Actually I did this first in response to a new PhD student David Sanders in 2000 when I'd just returned to Warwick, who wanted a project on emergence. More recently I went through Dobrushin's proof of ergodicity for weakly dependent probabilistic cellular automata and realised it could be expressed more nicely in terms of a metric on spaces of multivariate probabilities, which I have found useful in talking about the amount of emergence and the dependence on parameters. This is just a sample of things I've worked on and how I got into them. It is mostly serendipitous: just happening to pick up something where I could see I could do something, putting together things I'd already understood, interacting with interesting people.

Is stochastic dynamics closer to real systems than deterministic dynamics? Do you think that that is a fruitful direction for future work?

My view of stochastic dynamics is that the random terms represent aspects of the system that we choose not to attempt to model more accurately. In the absence of further knowledge or analytical ability this can be a sensible approach. Nevertheless, there are examples where the effect of some deterministic dynamics is rigorously equivalent to some noise process, the randomness being with respect to initial conditions, and then it makes sense to use the stochastic model. For example, a Langevin equation is widely used for the dynamics of slow degrees of freedom in a Hamiltonian system whose fast degrees of freedom are mixing. Anosov an I have scketched a derivation of this.

In the last few decades the number of active researchers and the quality of the mathematical work produced in Portugal has grown considerably. In your professional life have you ever had this perception?

It has been my privilege to interact with the dynamical systems group from Porto for at least 20 years and to supervise three PhD students from Portugal. And I've just taken on another one.

In contrast to older times, today mathematics is very much a collaborative effort. Do you have any preference between working alone or in teams? Is the challenge different?

There is still plenty of room in mathematics for single author research. But there are advantages to collaborations: broader perspective, shared work, wider dissemination.

Who is your favourite mathematician? Why?

I have many heroes, for example Moser, Arnol'd, Anosov and Sinai. I like what they have written and I like them as people (though unfortunately Arnol'd and Moser are no longer alive). Moser made many important advances in Hamiltonian dynamics; he was particularly nice to me, accepting me early in my career even though my approach was very non-standard mathematically and suggesting fruitful lines of research. Arnol'd was brilliant in a wide range of directions; he could be famously caustic but he was always nice to me and willing to answer my questions in considerable detail. Anosov I feel is a greatly under-rated mathematician: the insights he had in the 1960s about the Holder continuity of the foliations of hyperbolic dynamical systems and its implications for their measure theory are profound; I enjoyed making his acquaintance and showing him my mechanical Anosov system. Sinai I feel is the main architect of the theory of how deterministic dynamical systems can behave stochastically: he showed that the Markov partitions that had been constructed for special systems are a general feature of hyperbolic dynamical systems and that they give a correspondence of the dynamics to a generalisation of Markov processes called Gibbsian processes (which allow infinite-range but decaying memory). He has a very warm character and has been very supportive of my work. Going further back in time, I'd say Poincaré is my biggest hero: he developed so much interesting mathematics and presented it in such a readable way. And before him there was Newton, who was so creative, but apparently an awful character.

Detailed mathematical models in neurobiology—Storing information in membrane conductances dynamics

by **Eduardo Conde-Sousa*** and **Paulo Aguiar****

1. Introduction

Neurons are Nature's solution to the problem of information processing and information storage. Nervous systems have been engineered by evolution to sense information from the environment, process this information and store experiences for the purpose of improving future decisions. Ubiquitous in all these stages is the necessity of information buffers. In the case of mammals, there are different mechanisms providing storage in a wide range of time scales: from the ephemeral facilitation of a synapse to the life-long memories of childhood. As expected, neuronal dynamics are an extremely rich subject from a mathematically point of view. In this paper we focus on a model for a short-term memory mechanism called *working memory*. Regions of the mammal brain engaged in providing this functional resource are capable of retaining neuronal spatial patterns of activity for the duration of a few seconds. Basically, working memory provides a temporary buffer where information is held for short-time, while it is being actively used in cognitive tasks; this information can then be passed on to longer-term storage mechanisms or be simply discarded and forgotten. We humans use our working memory system when we temporarily retain a phone number or a name, when we mentally perform an arithmetic calculation, or when our wives tell us by phone the grocery list.

Our goal in this article is to give a glimpse into some of the methodologies used in theoretical neuroscience targeting a particular problem: to describe a mathematical model, closely fitted into the biophysical constrains of the nervous system, that helps understanding how working memory can be produced in a network of neurons. Our approach is different from other working memory models [1] in the sense that it does not rely on synaptic plasticity[1] nor connectivity structure to store information. In our model we store information in the dynamical states of the neuron's membrane conductances. An important feature in working memory systems is that it is possible to retain complex activity patterns after a single exposure to the stimuli. This constrain is better supported by the time scales found in conductances dynamics, than by synaptic plasticity temporal properties, even if we take into account short-term plasticity mechanisms.

In a population of N interconnected neurons engaged in working memory, we define as information content the particular subset of neurons that are co-activated

{1} Synapses are the structures that mediate most of the communication and transfer of signals between neurons. A strong synapse produces a large signal in the target neuron while a weak synapse will produce a small response. By modulating the synaptic strengths it is possible to both store information and to change the computational/functional capabilities of populations of neurons. The present dogma in neuroscience is that information is stored in the efficacy, or strength, of synapses.

* Faculdade de Ciências da Universidade do Porto
** Centro de Matemática da Universidade do Porto

at a given time. We assume that different sensory/perceptual configurations produce in this population different patterns of active units. In the neuronal population, the units not belonging to the memory pattern have low frequency stochastic activity (0.5Hz) while the units belonging to the pattern have a higher frequency activity (20Hz). The sizes of these patterns, i.e. the number of active units in any pattern, is considered to be roughly the same, which is in accordance with the notion of activity level control in neuronal circuits. The population can act as a working memory system if, after a short-period of a few hundred milliseconds where a subset of neurons is consistently co-activated (the duration of a "one-shot" stimuli, such as hearing a number a single time), this spatial pattern of activity is auto-preserved after the stimuli has been removed, for a duration of several seconds. In addition to this core property, our working memory model has to satisfy the following conditions:

- stochastic activations of spurious neurons should not be stored nor should affect the stored pattern
- the retained activity pattern should be stable for several seconds
- an inhibitory input within physiological values should be able to clear the memory pattern and restore the network to its basal, low frequency, stochastic firing
- deactivation of isolated neurons in the pattern should not compromise the rest of the pattern's integrity

This article is organized in the following way. First we describe in detail the mathematical model used to set the dynamics for each neuron individually, which parameters are used and how the numerical simulations are performed. The following section describes how the neuronal population is assembled, what network architecture is used and the properties of the synaptic connectivity. The following two sections describe results of the model: first we present results regarding the single neuron model, after that we present the results regarding the collective behavior of the neuronal population as a working memory system. We conclude with some final remarks.

2. Single Neuron Model

The neuronal dynamics are set using the Hodgkin-Huxley (HH) formalism in order to produce biophysically accurate descriptions of all neuronal conductances. Neurons are modeled as a single cylindrical compartment of length $L = 20\mu m$ and diameter $\text{diam} = 20\mu m$. That is, given the context and the questions being addressed, there are no *a priori* reasons to assume a special role to be taken by the spatial properties of the neuron. Therefore, the complex neuronal tree topology is collapsed and pointwise neurons are considered—hence the main variable is time only. Together with the leakage current and synaptic currents, a set of four ionic currents are considered in the membrane potential model. In addition to the canonical delayed rectifier potassium current and transient sodium current present in the HH equation, our model adds two more currents: a calcium current, $I_{Ca,L}$, which produces an influx of calcium whenever the membrane potential is becoming depolarized, and a nonspecific cationic current which is dependent on the intracellular calcium concentration, I_{CAN}. Together, these two currents can act synergetically to prolong depolarization in the membrane potential. These are currents that are known to exist in many neuronal types in the nervous system [2]. All ionic current dynamics are taken from Senselab [3] database. The time evolution of the membrane potential is described by the equation:

$$C_m \dot{V} = -I_L - I_{Na} - I_{Kdr} - I_{Ca,L} - I_{CAN} - I_{syn}$$

where $C_m = 1\mu F/cm^2$ is the membrane capacitance; V represents the membrane potential in mV; $I_L = g_L \times (V - E_L)$ is the leakage current, where $g_L = 4.2 \times 10^{-5} S/cm^2$ is the leakage conductance and $E_L = -65\text{mV}$ is the leakage reversal potential; I_{Na} and I_{Kdr} are the transient Na^+ and K^+ currents responsible for action potentials; $I_{Ca,L}$ is the high-threshold Ca^{2+} current and I_{CAN} is the intracellular calcium concentration nonspecific cation current mentioned earlier; finally, I_{syn} is the sum of all synaptic currents impinging on the neuron.

All numerical analysis/simulations were preformed in the simulation environment NEURON [4].

2.1. Sodium and Potassium currents (I_{Na} and I_{Kdr})

The fast Na^+ and K^+ currents are modeled according to the canonical Hodgkin-Huxley kinetics [5] with small modifications proposed by Traub and Miles to model hippocampal pyramidal cells [6]. The key parameters are: maximal sodium conductance $\bar{g}_{Na} = 80\text{mS/cm}^2$, maximal potassium conductance $\bar{g}_K = 20\text{mS/cm}^2$, sodium reversal potential $E_{Na} = 50\text{mV}$ and potassium reversal potential $E_K = -70\text{mV}$.

The model for these currents consists of:

$$I_{Na} = \bar{g}_{Na} \times m^3 \times h \times (V - E_{Na})$$
$$I_{Kdr} = \bar{g}_K \times n^4 \times (V - E_R).$$

The kinetic equation for the gating variables is

$$\dot{y} = -\frac{y - y_\infty(V)}{\tau_y(V)}.$$

where

$$y_\infty = \frac{\alpha_y}{\alpha_y + \beta_y},$$

$$\tau_y = \frac{1}{\alpha_y + \beta_y}.$$

and $y \in \{m, h, n\}$.

The activation and inactivation gate functions are:

$$\alpha_m = \frac{0.32 \times (73 - V)}{\exp\left(\frac{73-V}{4}\right) - 1}.$$

$$\beta_m = \frac{0.28 \times (V - 100)}{\exp\left(\frac{V-100}{5}\right) - 1}$$

$$\alpha_h = 0.128 \times \exp\left(\frac{72 - V}{18}\right)$$

$$\beta_h = \frac{4}{1 + \exp\left(\frac{95-V}{5}\right)}$$

$$\alpha_n = \frac{0.032 \times (75 - V)}{\exp\left(\frac{75-V}{5}\right) - 1}$$

$$\beta_n = 0.5 \times \exp\left(\frac{70 - V}{40}\right).$$

2.2. High-threshold Ca^{2+} current($I_{Ca,L}$)

The high-threshold $I_{Ca,L}$ current is modeled according to the equation [7]:

$$I_{Ca,L} = \bar{p}_{Ca,L} \times m^2 \times \text{GHK}(V, cai, cao).$$

were $\bar{p}_{Ca,L} = 0.03\text{cm/s}$ is the Ca^{2+} membrane permeability, cai and cao are respectively the intracellular and extracellular calcium concentration, and GHK is the Goldman-Hodgkin-Katz equation.

The kinetic equation for the activation variable is

$$\dot{m} = -\frac{m - m_\infty(V)}{\tau_m(V)}$$

where

$$m_\infty = \frac{1}{1 + exp(\frac{V+10}{-10})}$$

$$\tau_m = \frac{1}{\alpha_m + \beta_m}$$

$$\alpha_m = \frac{1.6}{1 + exp(-0.072 \times (V - 5))}$$

$$\beta_m = 0.02 \times \frac{1.31 - V}{1 - exp\left(\frac{V-1.31}{5.36}\right)}.$$

2.3 Intracellular calcium dynamics

The dynamics of the intracellular calcium concentration, denoted as cai, are modeled by a fast removal process due to an active pump, and by calcium entry which is due to the current $I_{Ca,L}$, as described in [8].

The used parameters are:

$depth = 0.1\mu\text{m}$

$cai_\tau = 1\text{ms}$

$cai_\infty = 5 \times 10^{-5}\text{mM}$

2.4. Ca^{2+} dependent nonspecific cation current (I_{CAN})

The adopted model for Ca^{2+}-dependent nonspecific cation current [9] is described as:

$$I_{CAN} = \bar{g}_{CAN} \times m^2 \times (V - E_{CAN})$$

with parameters $\bar{g}_{CAN} = 0.01\text{mS/cm}^2$ and $E_{CAN} = 0\text{mV}$. For our version of the model we modified the middle point of the activation function to 0.5×10^{-3} (before was 1.0×10^{-3}). This change allowed a small increase in the sensibility of this current to lower concentrations of intracellular calcium.

2.5 Synaptic Current

The synaptic current is modeled by the sum:

$$I_{syn} = \Sigma_i g_{syn,i} \times \left(V - E_{syn,i}\right)$$

where i runs over the set of pre-synaptic neurons. In other words, the term I_{syn} aggregates the currents from all synapses established with a particular neuron. All synapses in the model are excitatory, and their dynamics are modeled according to the biological NMDA synapse type. The core synaptic conductance profile is modeled by a dual exponential function:

$$g_{syn}(t) = \bar{g}_{syn} \cdot a\left[e^{-\frac{t}{\tau_{decay}}} - e^{-\frac{t}{\tau_{rise}}}\right]$$

where $g_{syn}(t)$ represents the synaptic conductance after t milliseconds of the synaptic activation and a is chosen so that the maximum value of g_{syn} matches $\bar{g}_{syn}$, the maximum synaptic conductance. The values for the rising time constant τ_{rise}, the decay time constant τ_{decay} and the synaptic reversal potential E_{syn} are: $\tau_{rise} = 5.0\,[\text{ms}]$, $\tau_{decay} = 70.0\,[\text{ms}]$ and $E_{syn} = 0.0\,[\text{mV}]$.

The NMDA synaptic current has the property of depending on the post-synaptic membrane potential: independently of the synaptic activation by the pre-synaptic neuron, an effective synaptic current will only be elicited if the post-synaptic membrane is sufficiently depolarized. In other words, this type of synapses act as an "AND" operator and has strong functional implications in the dynamics of neuronal networks. We follow a well established model and represent the NMDA synaptic conductance multiplying the dual exponential conductance profile by a factor representing the magnesium

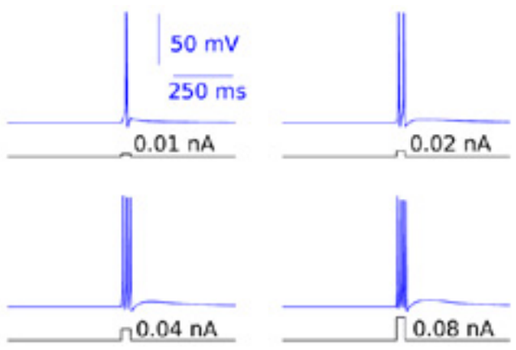

Figure 1.—Membrane potential response (in blue) to 40ms constant current stimuli of different amplitudes (in black).

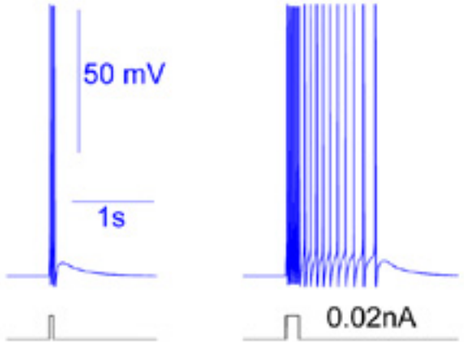

Figure 2.—Two electrode currents are injected in the neuron with amplitude of 0.02nA. The stimulus have a duration of 50ms (left) and 150ms (right). With a 150ms current injection the neuron sustain activity for a period of 900ms, after the end of the current injection. When the current injection is shorter, this period of sustained activity is non existing.

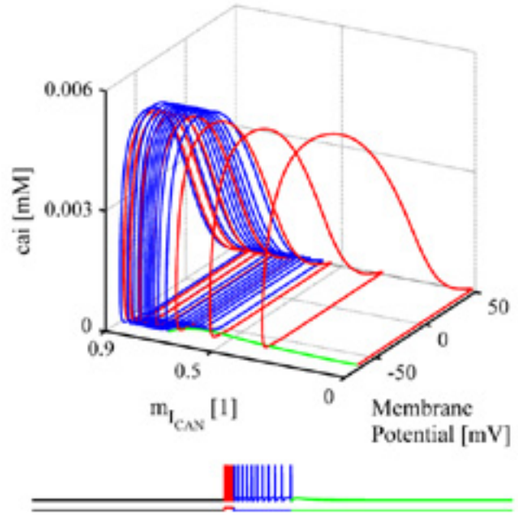

Figure 3.—An electrode current is injected in the neuron with duration 150ms and amplitude 0.02nA. The upper panel contains the phase space with variables $m_{I_{CAN}}$ (activation variable of CAN current), cai (intracellular calcium concentration [mM]) and membrane potential [mV]. The middle panel contains the membrane potential time evolution and the lower trace corresponds to the electrode current injected. For every new action potential, the activation variable $m_{I_{CAN}}$ increases (red trace). After the end of the current injection, the I_{CAN} activation variable slowly decreases to $m_{I_{CAN}} \approx 0.7$ (blue trace) and during a considerable amount of time, acting synergetically with the $I_{Ca,L}$ current, it is sufficient to sustain activity in the neuron. After this period, the depolarization induced by I_{CAN} is not sufficient to generate new action potentials and the membrane potential converges to the -65mV equilibrium potential (green trace).

block which characterize the post-synaptic dependence [10]. The NMDA model also accounts for the ratio of calcium current to total current [11] flowing through these channels as they introduce a relevant contribution to the increase of the intracellular calcium concentration.

3. Network topology

Working memory is a emergent property of the collective behavior of specific populations of neurons. The communication between neurons is determined by the connectivity matrix and in this model we use random connections to set the network architecture. Given two neurons, i and j, the probability of a synapse from pre-synaptic neuron i to post-synaptic neuron j is $P(i \to j) = ConnRate$, where $ConnRate$ represents the predefined connectivity rate of the model. The highest values in the mammalian brain are close to 30%, in regions with dense recurrent connections such as area CA3 in the hippocampus. As a central goal in this model is to store new information without involving synaptic changes, all peak conductances are taken from a common distribution and are then fixed for all numerical simulations.

While not plastic, the absolute values of the synaptic conductances are crucial in setting the activity level of the network. Two constraints are used to quantify the synaptic peak conductances, and therefore constraint all connections in the network:

1. one neuron must be able to fire stochastically, without entering a state of persistent activity due to interactions with active neurons;
2. when consistently excited, one neuron must be able to sustain activity for a period of tens of seconds as a result of the interactions with other active neurons.

By "consistently excited" we mean a series of coherent excitations in a small time window. The size of time window has to be balanced between small enough to be compatible with the notion of "one-shot learning" and big enough to make the probability of stochastic activations producing such an excitation profile virtually zero. A length of 200ms is chosen for the stimulation time window.

4. Results

For clarity purposes the results are separated into single neuron dynamics and population's collective behavior, where the emergence of a working memory system is analyzed.

4.1 Single neuron firing properties

In the absence of stimulation currents and stochastic noise, the neuron's membrane potential rests in the stable equilibrium point of about –65mV. Conversely, when a current of amplitude 0.01nA is injected for a period of 40ms to an isolated neuron an action potential (AP) is produced. Higher current amplitudes naturally lead to more APs in the same time period (see Fig. 1).

Each AP, or simply *spike*, results from the fast, but transient, Na^+ current and from the delayed rectifier K^+ current. Every time a spike is generated, the high-threshold calcium current activates and the intracellular calcium concentration rises. However, for short stimulation intervals like this one of 40ms, the slowly adapting I_{CAN} activation variable (long time constant) suffers little or no variation, leading to a negligible change in the I_{CAN} current. Thus, the dynamics of the neuron's membrane potential can be seen mainly as a result of the well know and well studied interaction between I_{Na} and I_{Kdr} currents. This is the situation where the neuron fires due to stochastic network activations or to very short, isolated and non-consistent external stimulation.

On the other hand, longer, consistent activations leading to several spikes with short latency give rise to a different behavior in the neuron's currents dynamics. The consecutive activation of the high-threshold calcium current generates a progressive increase in the I_{CAN} activation variable. The long time constant of the I_{CAN} activation variable enables a coarse integration leading to values close to 1.0. For a stimulation period of 150ms, the I_{CAN} activation variable reaches values in $m \in [0.85; 0.9]$ which are enough to sustain the activity for a period of several hundred milliseconds (see Fig. 2). A consistent stimulation in a time window of 100 – 200ms is compatible with the "one-shot learning" paradigm.

The synergy between I_{CAN} and $I_{Ca,L}$ can be better appreciated in a phase graph (Fig. 3), where the axis are the neuron's membrane potential, the I_{CAN}'s activation variable m and the calcium's intracellular concentration which is heavily modulated by $I_{Ca,L}$.

It is important to emphasize that in order to consistently excite one neuron, the variable $m_{I_{CAN}}$ must rise

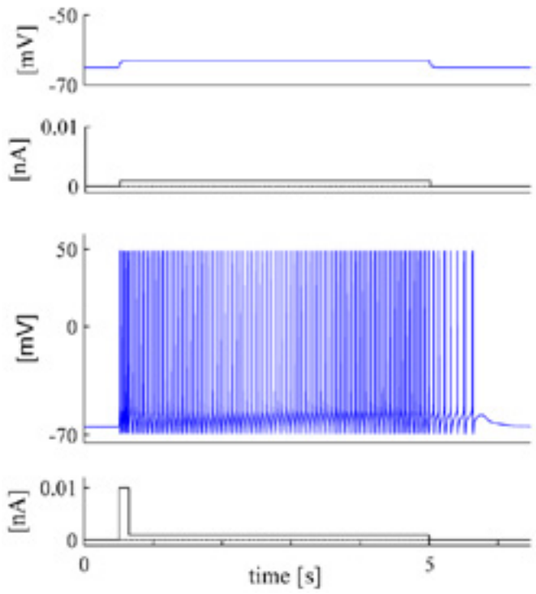

Figure 4.— A residual current injection of 0.001nA only produces a small depolarization in the membranes potential and is incapable of eliciting APs (upper traces). On the other hand, if this residual current follows a 150ms, 0.01nA amplitude core stimulus, the other way vanishing activity now becomes persistent (lower traces).

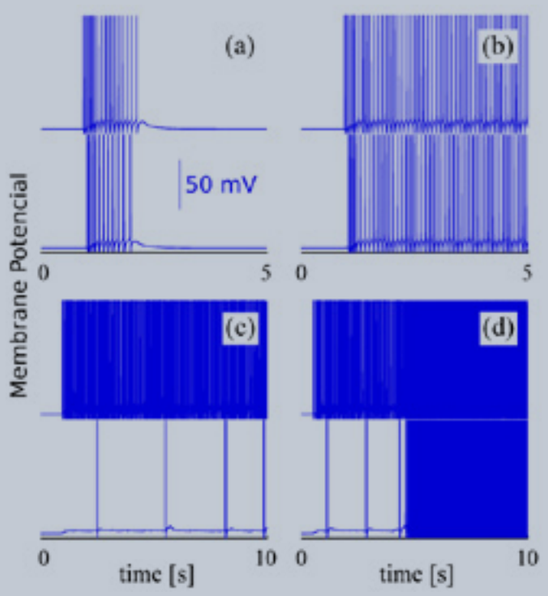

Figure 5.—Parametrization of the NMDA peak conductances w. Two neurons connected through a single NMDA synapse are used to assess the proper synaptic conductance values. A synaptic value of $w=4.0\times10^{-5}\mu S$ is insufficient to provide enough recurrent excitation to sustain activity after the short period of stimulation on a small fraction of the population; the membrane potential traces for the two neurons connected through such w are shown in panel **(a)**. Above $w=5.0\times10^{-5}\mu S$, the recurrent connections are already sufficient to preserve the activity pattern; again the membrane potential traces for the neurons connected through the new w are shown in panel **(b)**. This proper functional behavior is maintained up to $w=20.0\times10^{-5}\mu S$; the activity in the neuron belonging to the memory pattern does not propagate to other neuron even if they are subject to stochastic activations—panel **(c)**. Higher synaptic conductance values, such as $w=22.0\times10^{-5}\mu S$, start to invoke spurious activations and instability on the activity pattern; the activity in the neuron belonging to the memory pattern is now capable of recruiting additional neurons, thus corrupting the working memory—panel **(d)**.

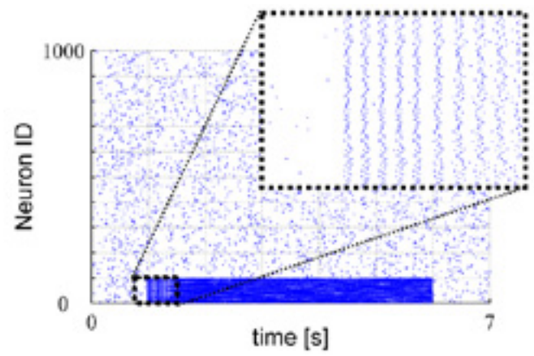

Figure 6.—Working memory in action. A sub-population of 100 neurons is activated and is capable of sustaining its activity for a long period of time without becoming corrupted (by loosing or adding elements).

enough (above 0.7). This *CAN* current is only activated by rising the internal concentration of calcium, which in turn depends on the existence of APs. Thus, the stimulus current must be sufficient to trigger a sequence of APs during a period between 100 and 200ms, depending on the achieved firing rate. Lower firing rates require longer periods of consistent stimulation. For example, with a 150ms and 0.02nA amplitude current injection, the neuron fires five times over a period of approximately 120ms (corresponding to an average firing rate of 30Hz) which is sufficient to sustain the activity for a few hundreds of milliseconds after the stimulation finishes. However, if a small residual current is provided after the stimulus ends, the neuron can retain its activity for much longer periods of time (Fig. 4). This property is of considerable importance as it sets the conditions in which a working memory system can work.

4.2 Network behavior

Unless otherwise stated, all presented network results refer to simulations with a population of 1000 neurons, with a recurrent connectivity rate of 25%. The stimulation protocol consists of exciting 100 neurons (10% of the population), creating the so called memory pattern of activity. The stimulation lasts for 200ms and generates 5 spikes on each neuron (individual firing rate of 20Hz). All induced spikes are not completely synchronized: a uniform random jitter of ±10ms is introduced to emphasize the robustness of the system to small amounts of noise. This robustness comes mainly from the long-lasting NMDA conductance profiles and from the fact that the passive properties of neuron membrane act as a low-pass filter with a time constant, in the case of this model's parameters, of ≈ 24ms (obtained from C_m/g_L). These two mechanisms significantly enlarge the integration time scale for the synaptic inputs.

In addition to the spike jitter in the memory pattern activation, noise is constantly provided to all neurons, belonging or not to the memory pattern. Noise is introduced as stochastic activations following a Poisson process with an average interspike interval of 2000ms (0.5Hz), in agreement with cortical neurons experimental data.

In the connected population, the residual stimulation required to sustain the memory pattern is provided by the recurrent connections. The NMDA's synaptic peak conductances are therefore of noteworthy importance. The calculated range of values which satisfy the two constraints mentioned in section 3, given all neuronal model parameters, is $[5\times10^{-5}, 20\times10^{-5}]\mu S$ (see Fig. 5). These values correspond to the *total* NMDA synaptic conductance required to drive the target neuron in this safe zone and are therefore independent of the population size; in other words, they represent the target value for the sum of all synaptic conductances and are obtained considering a complete synchrony in the synaptic activations. This is a strong assumption but, again, the long-lasting NMDA conductance profiles and the long membrane's time constant produces a synchronicity time window in the order of a few tenths of milliseconds. This interval encapsulates the variability in the memory pattern activations and renders irrelevant the need for complete, sub-millisecond, synaptic synchronization. The calculated values for the total synaptic conductance under the synchrony assumption are then safely used as estimators for the total synaptic conductance under less stringent synchronicity constraints.

While the required total synaptic conductance is a function of the neuron's parameters and independent of the population size, the individual NMDA synaptic conductances depend on the number of synaptic inputs each neuron receives. This number follows a binomial distribution with parameters N, the population size, and *ConnRate*, the connectivity rate.

The working memory behavior of the system can be visualized in a raster plot, where the spikes of all neurons are represented as dots (Fig. 6). The consistent but short activation of a constellation of neurons in the population forms a memory activity pattern which sustains for several seconds due to the synergy between the $I_{Ca,L}$ and I_{CAN} currents, and the stabilizing current provided by the recurrent connections. Two relevant points worthwhile mentioning is that both the activity pattern firing frequency (in the range of 15–20Hz) as well as the magnitude of the inhibitory conductance necessary to reset the memory pattern (in the range of 0.1μS for a duration of 200ms—compatible with $GABA_B$) are in accordance with neurobiological data [2].

4.3 Model scaling

The simulation results shown use a population of 1000 neurons. It is interesting to notice that as the number of neurons rises, our working memory model becomes more robust to variability in the NMDA's peak conductances.

Given the synaptic constraints (see Fig. 5), we can conclude that a neuron belonging to the activity pattern must receive a total synaptic conductance of, at least, $5\times10^{-5}\mu S$ from the other neurons belonging to the pattern. Therefore, if m is the minimum number of connec-

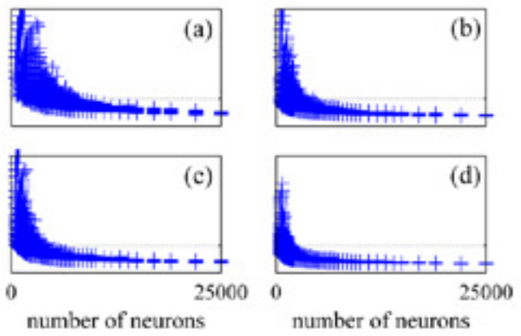

Figure 7.—Larger population sizes produce more robust working memory systems. Each graph represents the value of M/m obtained for randomly generated connectivity matrices as a function of the total number of neurons in the population (between 500 and 25000), the percentage neurons belonging the activity pattern (5% in **(a)** and **(b)**, and 10% in **(c)** and **(d)**), and the connectivity rate (10% in **(a)** and **(c)**, and 20% in **(b)** and **(d)**). For each population size, 500 samples are drawn. The dashed line marks the value M/m=4 below which the variability in the synaptic conductances becomes better contained within the calculated bounds.

tions each neuron in the pattern receives from other neurons in the pattern, the average synaptic efficacy must be $\geq 5 \times 10^{-5}/m$. On the other hand, a neuron outside the activity pattern must not be activated by the neurons in the pattern; i.e. it must not receive more than a total synaptic conductance of $20 \times 10^{-5}\mu S$. If M is the maximum number of connections each exterior neuron receives from neurons belonging the pattern, than the average synaptic efficacy must be $\leq 20 \times 10^{-5}/M$. Thus, the average synaptic efficacy must be between $5 \times 10^{-5}/m$ and $20 \times 10^{-5}/M$ which is only possible if $5 \times 10^{-5}/m \leq 20 \times 10^{-5}/M$. This means that $M/m \leq 4$.

As the population size grows, the fluctuations in the number of input synapses each neuron receives becomes less relevant (scales with $1/\sqrt{N}$) and the excitation reaching neurons inside the memory pattern, and outside, becomes more homogeneous. Less variability in the total synaptic conductances means that corruption of the memory activity pattern becomes less probable. A comparison of the population sizes required to obtain highly robust working memory systems, as a function of the pattern size and *ConnRate*, is shown in Fig. 7.

5. Final remarks

We have shown how detailed biophysical models and their numerical analysis can be used to shed light to complex problems in neurobiology. These type of models are not simply a mathematical challenge: their proximity to biology makes them ideal to construct new hypothesis, produce predictions, catalyze new experiments and ultimately improve our understanding of how our brains can process and store information.

Acknowledgments

Research funded by the European Regional Development Fund through the programme COMPETE and by the Portuguese Government through the FCT—Fundação para a Ciência e a Tecnologia under the project PEst-C/MAT/UI0144/2011.
Eduardo Conde-Sousa was supported by the grant SFRH/BD/65633/2009 from FCT.

References

[1] D. Durstewitz, J. K. Seamans, and T. J. Sejnowski. Neurocomputational models of working memory. *Nat Neurosci*, 3 Suppl:1184–1191, Nov 2000.

[2] E. R. Kandel, J.H. Schwartz, and T. M. Jessell. *Principles of Neural Science*. Mc Graw Hill, 2000.

[3] Chiquito J Crasto, Luis N Marenco, Nian Liu, Thomas M Morse, Kei-Hoi Cheung, Peter C Lai, Gautam Bahl, Peter Masiar, Hugo Y K Lam, Ernest Lim, Huajin Chen, Prakash Nad- karni, Michele Migliore, Perry L Miller, and Gordon M Shepherd. Senselab: new developments in disseminating neuroscience information. *Brief Bioinform*, 8(3):150–162, May 2007.

[4] M. L. Hines and N. T. Carnevale. The neuron simulation environment. *Neural Comput*, 9(6):1179–1209, Aug 1997.

[5] A. L. Hodgkin and A. F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*, 117(4):500–544, Aug 1952.

[6] R. D. Traub and R. Miles. Multiple modes of neuronal population activity emerge after modifying specific synapses in a model of the ca3 region of the hippocampus. *Ann N Y Acad Sci*, 627:277–290, 1991.

[7] D. A. McCormick and J. R. Huguenard. A model of the electrophysiological properties of thalamocortical relay neurons. *J Neurophysiol*, 68(4):1384–1400, Oct 1992.

[8] A. Destexhe, A. Babloyantz, and T. J. Sejnowski. Ionic mechanisms for intrinsic slow oscillations in thalamic relay neurons. *Biophys J*, 65(4):1538–1552, Oct 1993.

[9] L. D. Partridge and D. Swandulla. Calcium-activated non-specific cation channels. *Trends Neurosci*, 11(2):69–72, Feb 1988.

[10] C. E. Jahr and C. F. Stevens. A quantitative description of nmda receptor-channel kinetic behavior. *J Neurosci*, 10(6):1830–1837, Jun 1990.

[11] N. Burnashev, Z. Zhou, E. Neher, and B. Sakmann. Fractional calcium currents through recombinant glur channels of the nmda, ampa and kainate receptor subtypes. *J Physiol*, 485 (Pt 2):403–418, Jun 1995.

Modeling and simulation of the human cardiovascular system

by **Alexandra Bugalho de Moura*** and **Adélia Sequeira****

Abstract.—The use of mathematical modeling and numerical simulation to study blood circulation and related pathologies is an active interdiciplinary field of research. It has a great social and economical impact mainly due to cardiovascular diseases, that represent one of the leading causes of death and morbidity in industrialized countries.

Due to the complexity of the human cardiovascular system, the use of computational models to study blood flow in healthy and pathological situations is a challenge to mathematicians and engineers. Nevertheless, it constitutes nowadays a reliable tool which is increasingly used in clinical applications, such as the placement of stents in arteries with atherosclerotic plaques, or the understanding of aneuerysm growth and rupture.

In this article some of the fundamental aspects of mathematical modeling and numerical simulation of blood circulation will be described, highlighting in particular the pathological case of cerebral aneurysms.

1. Simulating blood circulation: a challenge to mathematicians

Over the last years, the development and application of mathematical models, seconded by the use of efficient and accurate numerical algorithms, has allowed for impressive progresses in the understanding of the human cardiovascular system, in both healthy and pathological situations [5,12,9]. The developments in scientific computation techniques and computers capacity have also contributed to patient-specific studies, providing valuable clinical information in the perspective of diagnosis, treatment or surgical planning [5,15,12,9,13,14]. Indeed, the increasing demand from the medical community for scientifically rigorous investigations of cardiovascular diseases has been a major impulse to the progress in this field. However, modeling and simulating the human circulation still remains a very difficult and challenging task. The geometrical structure of the vascular tree and the heterogeneous composition of blood, the mechanical and biochemical interactions between blood and the vessel walls, the pulsatile nature of blood flow, together with auto-regulation processes and the link between global and local circulation, are extremely complex physiological phenomena. Therefore, it is impossible to construct a three-dimensional (3D) mathematical model of the circulatory system including all those characteristics, and therefore simplifications are mandatory. On the other hand, it is recognized that cardiovascular pathologies, like atherosclerosis or aneurysms, are closely related with local hemodynamics, such as areas of flow

Keywords.—Mathematical modeling, numerical approximation, computer simulations, computational fluid dynamics (CFD), blood flow, cardiovascular system, fluid-structure interaction, geometrical multiscale modeling, aneurysm.

* Department of Mathematics and CEMAT, Instituto Superior Técnico, Technical University of Lisbon.
E-MAIL: xiluva@gmail.com

** Department of Mathematics and CEMAT, Instituto Superior Técnico, Technical University of Lisbon.
E-MAIL: adelia.sequeira@math.ist.utl.pt