# Location, location, location (and density) of gap junctions in multi-compartment models

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.

## ABSTRACT

Interneuronal networks are important in mediating several rhythmic brain states. Their interconnections include dendritic gap junctions which can give rise to various network patterns depending on their location and density. We develop full and reduced (two-compartment) multi-compartment models of hippocampal basket cells and examine two-cell networks of them. The location and density of the gap junctions determine if and when synchronous and phase-locked patterns arise. Comparison of the full and reduced network models allows us to obtain biological quantification of gap junction conductance values in the reduced models.

## SUMMARY

### Introduction

Gap junctions (GJs) are well-known portals of electrical, intercellular communication [3, 27]. They consist of twelve connexin (Cx) proteins, six of which form hemichannels or connexons. Neuronal GJ proteins (Cx36) have been identified and Cx36 knockout mice have been created [6, 14, 19]. Furthermore, there is direct anatomical evidence for the presence of GJs between the dendrites of basket cells in hippocampus [8].

A common cortical infrastructure is interneuronal networks of basket cells connected by both inhibitory synapses and GJs [2, 7, 8, 9, 10, 11, 17]. These interneuronal networks play central roles in mediating rhythmic patterns of different frequencies that are associated with various behavioural states [4, 26]. The importance of GJs in producing brain rhythms is currently an intense area of investigation using various approaches [6, 14, 16, 20, 22, 23]. Despite this, it is far from clear how GJs contribute to the output produced by interneuronal networks. To understand the potential role(s) of GJs in normal (and pathological) states, as expressed in brain rhythms, we need to understand how the location and density of GJs give rise to different dynamic network patterns.

Theoretical and modelling studies using simple neuronal caricatures clearly show that the effects of GJ-coupling are not straightforward. Synchronous, anti-synchronous, phase-locked and bistable patterns can be produced in GJ-coupled networks depending not only on GJ strength, but also details of the spike shape and frequency [1, 5, 15, 21]. To gain further insight from these studies, we need to be able to attribute biological quantification of the parameters used in them.

In this paper we develop two different multi-compartment models of hippocampal basket cells. The first is a full multi-compartment model and the second is a two-compartment model which represents a phenomenological reduction of the full model. We build two-cell networks of these models coupled via dendritic GJs and examine their network dynamics. The location and density of the GJs determines if and when synchronous and phase-locked patterns arise. By comparing the full and reduced network models we can obtain biological quantification of GJ conductance values in the reduced two-compartment models. In this way, theoretical insights obtained using simpler models can be interpreted in a more biologically relevant fashion.

## Models and Methods

*Full multi-compartment model:* A 372-compartment model was built using NEURON [13]. It is based on a hippocampal basket cell morphology taken from [12] and http://www.koki.hu/~gulyas/ca1cells. The soma contains sodium and potassium channels and the dendrites are passive. Electrophysiological responses and passive properties measured in basket cells [24, 18] were matched.

*Reduced multi-compartment model cell:* Two-compartment models were constructed using the following equations for a given cell:

$$\begin{aligned} C\,\frac{dV_S^i}{dt} &= I_{app} - I_{Na} - I_K - I_L - g_c(V_S^i - V_D^i) \\ C\,\frac{dV_D^i}{dt} &= -I_L - g_c(V_D^i - V_S^i) - \mathbf{g_{gap}}(\mathbf{V_D^i - V_D^j}) \end{aligned}$$

Parameters have the standard meaning. $V_{S/D}$ is the voltage in the somatic ($S$) or dendritic ($D$) compartment, $i, j$ are neuron indices referring to different neurons, and $g_c$ is the coupling between somatic and dendritic compartments. Parameter values for intrinsic currents are based on [25] and those of the full multi-compartment model.

*Two-cell networks:* Two-cell (homogeneous) networks of model cells coupled by GJs were constructed. GJs are modelled as shown by the boldfaced term in the equation above where $g_{gap}$ is the GJ conductance. In the full model cell, we selected three different locations on the dendritic tree where different densities of GJs were inserted. The dendritic GJ "location" in the reduced model networks is determined by the $g_c$ parameter. For each selected location, we created a reduced two-compartment model in which $g_c$ was adjusted to match the attenuated spike heights seen at the particular dendrite location in the full model. Networks of these reduced model cells are taken to correspond to GJs being located at the selected site in the full model. Three different intrinsic frequencies as determined by $I_{app}$ were examined in the full and reduced network models.

## Results and Conclusions

We know from previous modelling studies that with strong GJ-coupling, only synchronous behaviours will occur, but with weak GJ-coupling, bistable, anti-synchronous and other phase-locked patterns can arise [5, 15]. Our reduced network models produced such

behaviours. Specifically, as $g_{gap}$ increases (for a given location and intrinsic frequency), the network produces anti-synchronous, phase-locked (with decreasing phase lags) and synchronous output. Therefore, synchrony occurs with large $g_{gap}$, anti-synchrony with small $g_{gap}$, and phase-locked behaviours with intermediate $g_{gap}$. With higher intrinsic frequencies, larger $g_{gap}$ is needed to achieve synchronous behaviours and $g_{gap}$ does not have to be as small to obtain anti-synchronous behaviours. The further away the GJs were "located" in the reduced model, the easier it was to obtain anti-synchronous behaviours. Bistability was obtained in certain parameter ranges (e.g., far location, low frequency).

With the full network model, we obtained results that were similar to the reduced network models, except that the full span of behaviours (synchronous to anti-synchronous) could not be obtained for a given location and frequency within the (generous) physiological ranges examined. For example, synchronous behaviours did not occur when GJs were located at farther locations for higher intrinsic frequencies. In general, synchrony required stronger GJ-coupling (than for anti-synchrony) and occurred more easily in closer locations and with lower frequencies. Unlike the reduced models, we found that the full network model expressed an unexpected behaviour: Phase-locking with the same lag at both high and low $g_{gap}$ values. Interestingly, this behaviour occurred in a regime corresponding to bistability in the reduced model network.

To biologically quantify parameter values in the reduced network models, we matched phase-locked behaviours in the full and reduced models. When parameter values were converted (in terms of surface areas) for comparison, we found that $g_{gap}$ values in the reduced models were quantifiably similar to the full model only when $g_{gap}$ values were in a 10-100 pS window (depending on the particular frequency and location). If not, then $g_{gap}$ in the reduced model was either too small (for smaller phase lag patterns which occurred at larger $g_{gap}$) or too large (for larger phase lags which occurred at smaller $g_{gap}$). This occurs because the two-compartment model does not adequately capture the attenuation and the changing input resistance when GJs are opened in the full model. For smaller $g_{gap}$, the former reason dominates whereas for larger $g_{gap}$, the latter reason takes over to cause $g_{gap}$ in the reduced model to be inappropriate from a biologically quantifiable point of view. We could reasonably correct for these aspects by introducing an adjusting factor that was determined by comparing GJ currents in the reduced and full models. This factor ranged from about 0.02 to 50. In this way, biologically quantifiable values for $g_{gap}$ in the two-compartment models could be obtained. This quantification should allow us: (i) to gain more from theoretical studies performed using "simpler" models (e.g.,[15]) in which biological quantification of parameter values is difficult, and (ii) to explore larger network dynamics in physiologically relevant parameter regimes using reduced models.

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