Coupling effects in mouse and human β-cells networks: emergent dynamics

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Introduction

- β-cells in the endocrine pancreas are a typical example of coupled biological oscillators. In particular, published literature strongly indicates that direct electrical coupling, due to gap junctions, has a key role in synchronising cells activity, with beneficial effects on the insulin release [1 – 3].
- In this work we study the emergent dynamics of β-cells coupled networks in variable operating conditions and in different topologies. The aim is to investigate the observed interspecies variability in cellular architecture [4,5] and pathologically degenerate cases of connectivity from a functional point of view.
- We further study gap junction properties, mostly studied in rodents, in the human case [6,7], obtaining an estimation of the coupling conductance and analyzing its effects on the emergent behavior of small β-cells coupled clusters.

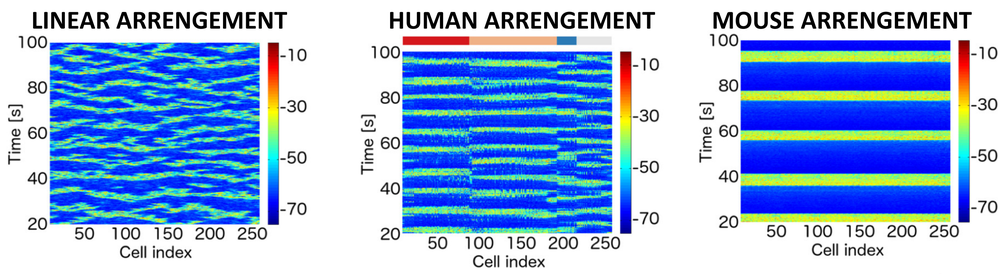
METHODS: MODELING

We adopt an Hodgkin-Huxley type modeling to reproduce β-cells electrophysiology, introducing a diffusive term in the membrane voltage dynamics to take into account gap junction currents:

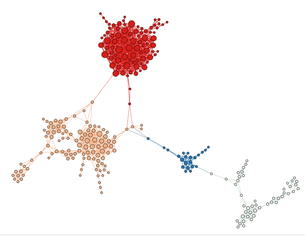
- A stochastic generalised SRK model [8] is used to reproduce the emergent dynamics of mouse and human β-cells networks, studying cells synchronisation in a physiological range of the parameters via a "functional network" approach.
- A deterministic electrophysiological model fine-tuned on human data [9] is used instead to estimate gap junction conductance between human β-cells and to analyse emergent electrical oscillations of small heterogeneous cubic clusters.

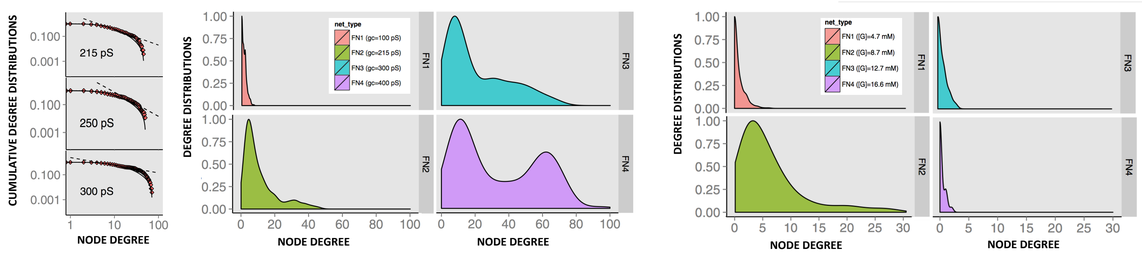
Results: structure-function analysis [10]

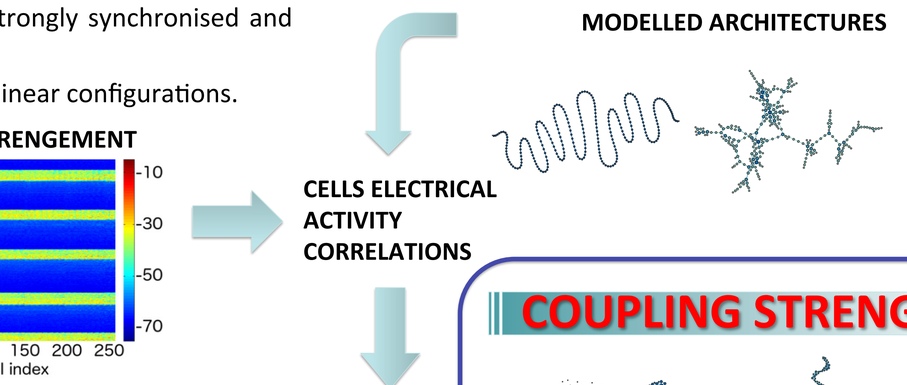
- ✓ Compact clusters resembling mouse β-cells arrangement induce a strongly synchronised and robust electrical activity.
- ✓ Synchronisation and bursting robustness is seriously compromised in linear configurations.



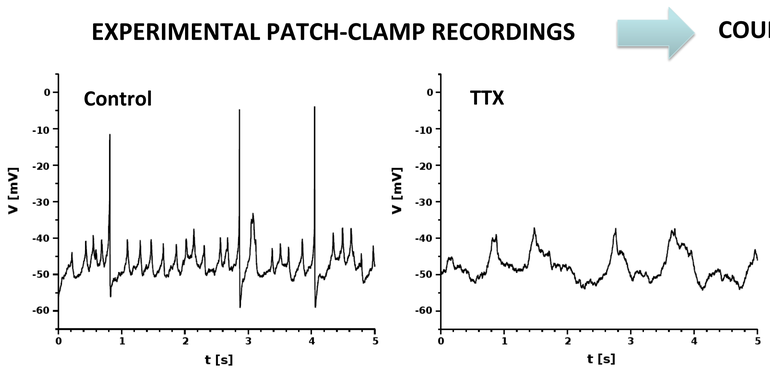
- ✓ Human β-cells architecture shows limited synchronisation, out of phase bursting oscillations and modularity in the emergent activity.
- ✓ Human functional networks are characterised by inhomogeneity in the degree distribution highlighting a scale-free-like topology. Such topological features are conserved only at physiological levels of the parameters.

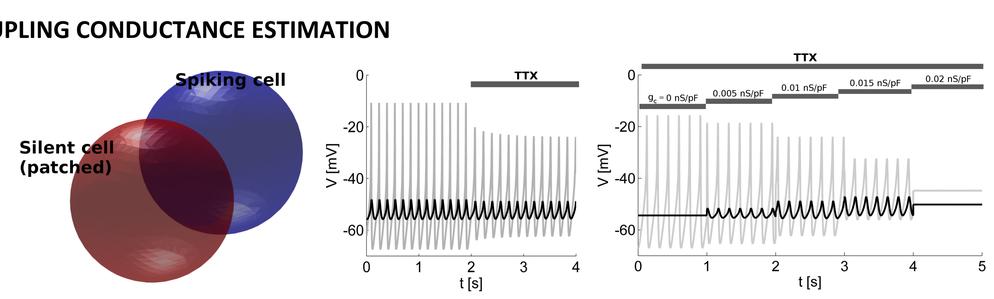




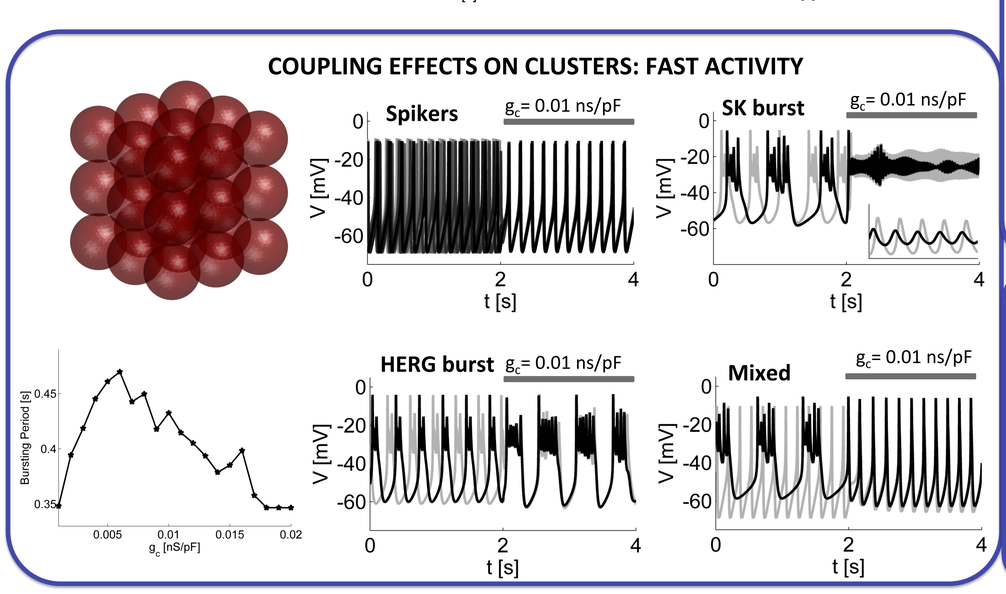


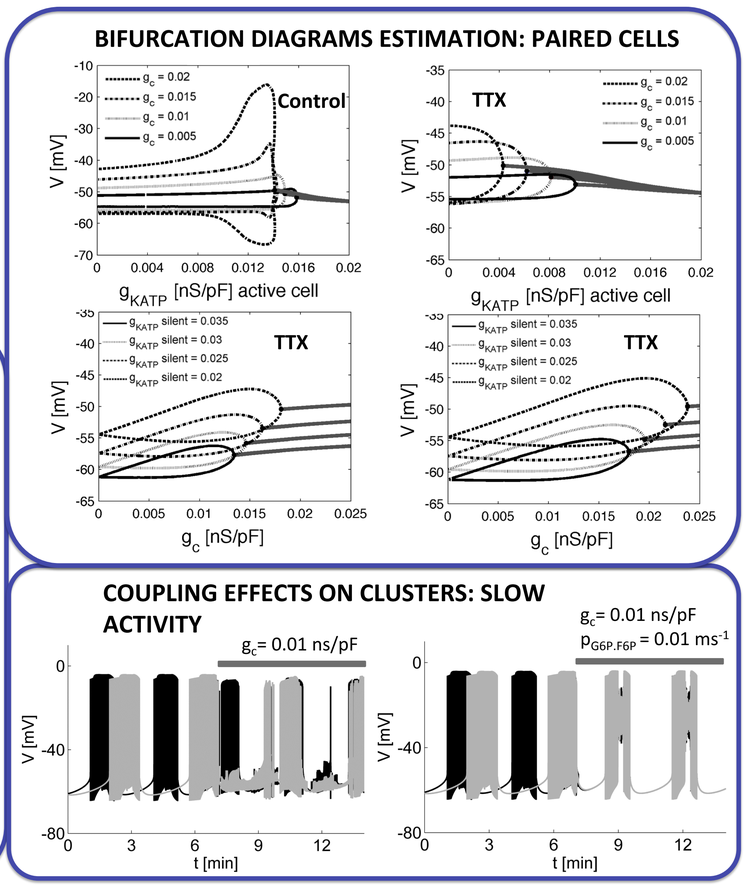
Results: gap junction coupling between human β-cells [11]





- ✓ Estimated gap junction conductance (0.01-0.02 nS/pF) is in line with measures reported for rodents [12].
- ✓ Cells coupling synchronises the spiking activity of small heterogeneous β-cells clusters.
- ✓ Bursting oscillations are altered by coupling.
- ✓ Coupling in mixed clusters of cells, showing both bursting and spiking endogenous activity, suppresses bursting oscillations.
- ✓ Slow bursting, driven by glycolytic oscillations, is affected by coupling. By considering both the sole electrical coupling and a combined electrical/metabolic coupling, patterns similar to the experimental ones [9,13] are recovered.





Conclusions and Future perspectives

The structure of β-cells network has a significative impact on the emergent synchronisation and functionality. Functional networks constructed with the model could be studied in this scenario in combination with experiments, where functional connectivities are limited to cross-sectional islet data [14]. Furthermore, gap junction conductance estimation between human β-cells obtained with a modelling approach is in line with reported measures for mouse [12] and numerical simulations suggest that it can alter emergent electrical activity. Experimental studies will be needed to validate these findings and further studies should be devoted to combining functional analysis with the electrophysiological model used for the estimation of the coupling conductance between human β-cells.

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