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Towards a Multi-scale Systems Biology Model of the Developing Heart

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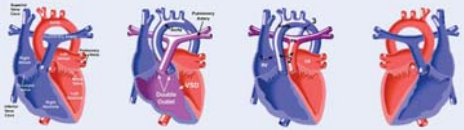
Rationale

Heart development consists of a series of sequential events:

Männer, J. (2000) Anat. Rec.

Aberrant looping results in various congenital heart diseases:



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The looping phase is governed spatio-temporally by complex subcellular regulatory networks [1, 2].

Despite the wealth of experimental data, the underlying mechanisms controlling looping phase are unclear.

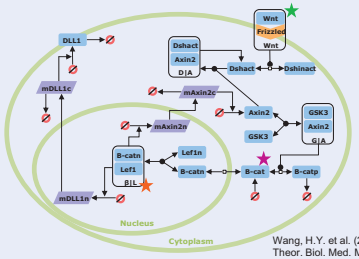
Aim

To study how the signalling pathways and gene regulatory networks **(subcellular level)** regulate cells' proliferation and growth **(cellular level)** and so contribute to the C-looping phase **(tissue level)**.

Methods

Multi-scale computational modeling:

Sub-cellular level

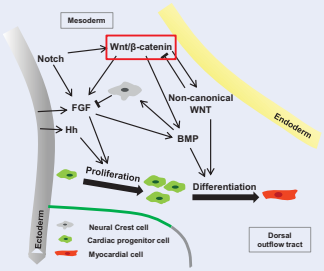


Wang, H.Y. et al. (2013) Theor. Biol. Med. Model.

Wnt/β-catenin signaling pathway

cellML

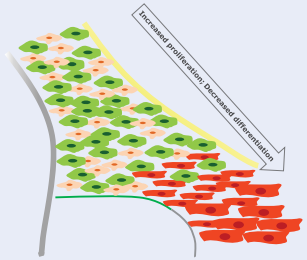
Cellular level



Cardiac progenitor cells' proliferation and differentiation is regulated by complex signaling pathways crosstalk

cellML

Tissue level



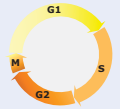
Cardiac progenitor cells' proliferation and differentiation into myocardial cells result in heart tube elongation

(Agent-Based Modeling)

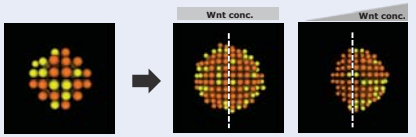
Results

- **Linking the Wnt signaling to the cell's proliferation.**

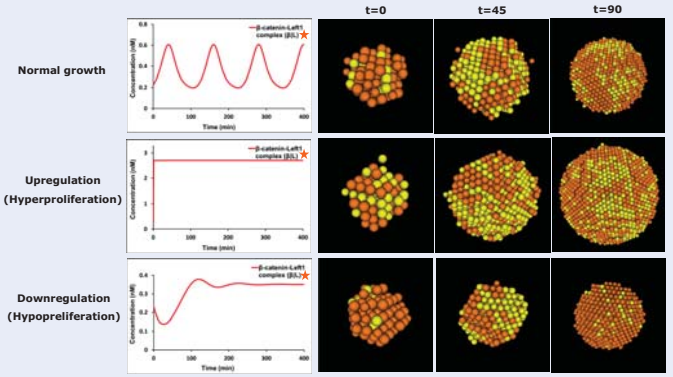
Wnt signal → β-catenin → β-catenin-Left1 complex (β|L) → target gene (Cyclin D2)



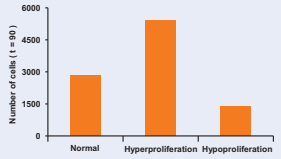
- **Growth in response to the constant and gradient Wnt signal strength.**



- **Growth in response to the normal and perturbed β-catenin expression.**



In silico results are consistent with experimental results on the role of Wnt/β-catenin in cardiac progenitor cells' expansion through FGF signaling [3].



Conclusion

This study will introduce a platform to study developmental systems in a multi-scale manner through:

- capturing emergent effects of inter-level and intra-level interactions across subcellular, cellular and tissue level.
- examining the effect of subcellular activity on morphology by in silico studies.

References

[1] Bruneau, B.G. (2008) Nature. 451, 943-948.
[2] Taber, L.A. (2006) Int. J. Dev. Biol. 50, 323-332
[3] Cohen, E.D., et al. (2007) J. Clin. Invest. 117, 1794-1804

Acknowledgements

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