Framework for Neurosphere Modeling under Phase-Contrast Microscope

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1 Problematic

One of the major recent research field in the biomedical domain lies in the understanding of stem cells. Sptem cells are characterised and identified by the expression of three properties: (i) the capacity to renew their population over a large period of time, (ii) the capacity to produce specialised cells of a particular tissue, and (iii) participate into the regeneration of tissue after injury. Present in high concentration during the foetal phase as they participate to its development, their number drastically diminish once the individual reach the adult state. They remaining stem cells, renamed somatic (or adult) stem cells, are present in different tissue of the body, and their existence and role raised multiple interrogations: Where do they come from? Do they participate in the regeneration process of some tissue? Can they produce specialised cells of a different host tissue? Is there a link between somatic stem cells and cancer cells? In the case of neural stem cells, somatic stem cells of the central nervous system, their characterisation and culture, *in vitro*, is done through the Neurosphere Formation Assay (NFA) experiment proposed by Reynolds and Weiss in 1992. The experiment consists in isolating neural cells extracted from the specific tissue of the central nervous system and place them in suspension in a dish for a defined period of time ($\tilde{5}$ days). In the case of the isolated cells are generic, they will inevitably die after a certain time. If the isolated cells are neural stem cells, the expression of their renewal and differentiation properties will lead to the formation of spherical agglomerate structure of cells called neurosphere. The question we ask ourselves is: Could the observation and the understanding of the formation process of neurosphere bring information to understand the role of neural stem cells and help us to better control their culture *in vitro* ?

2 Thesis Outline

This thesis concentrates its research efforts on the structure of the neurosphere during its formation. The dissertation will focus mainly on the design of a framework to observe neural stem cells at different stage of the formation assay and extract, through a modeling process, the three-dimensional structure of the neurosphere at the current observation. The framework (Fig. 1) is composed of three main process: (i) the analysis - extracting information from the microscope observation, (ii) the modeling - generating possible structural configuration of cells using information from the analysis process and *prior* knowledge of neurosphere, and (iii) the selection - use a 3D to 2D registration process to evaluate the generated model based on the

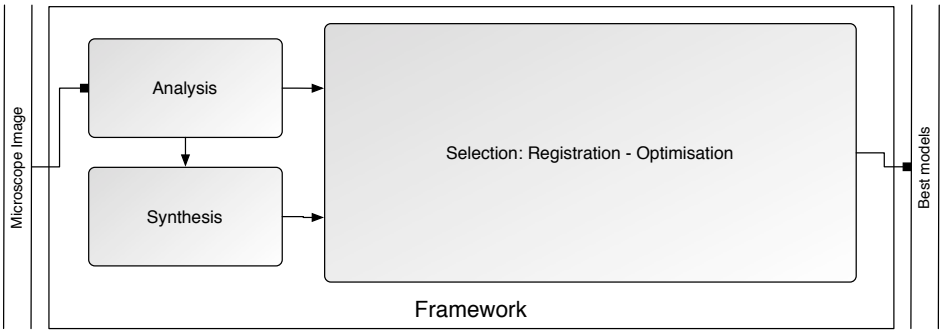
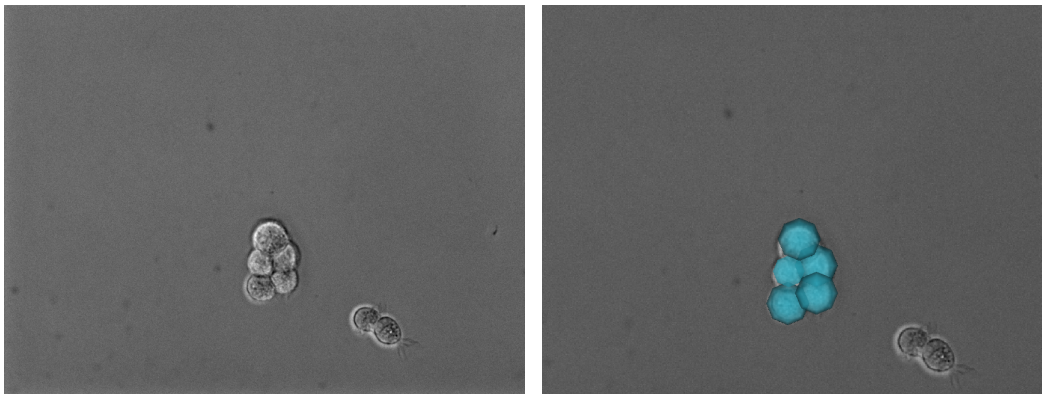


Figure 1: High-level framework for neurosphere modeling



(a) (b)

Figure 2: Example of a visualisation of the model of a 5-cells neurosphere configuration

microscope observation. The work is presented in four chapters, following the different parts of the framework. In the first chapter, we provide the background and motivation related to this doctoral work. The second chapter consists in the analysis process, in which the neurosphere is tracked, segmented and the visible cells are detected. The third chapter presents the three-dimensional modeling process. Two approaches are so introduced: an iterative mesh modeling using Delaunay mesh and an evolution construction model using evolution algorithm. The fourth chapter provides the selection process to score and rank the different generated model that are generated using a 3D to 2D registration process between the models and the observation, and an analysis of the results and the on the two methods.

3 Thesis Outcome

Leveraging our experience with traditional approach to biomedical imaging which rely on high content image analysis, this work proposes a method to determine the 3D cell configuration of a structure such as neurosphere, from a phase-contrast microscope 2D observation. Focussing on the structural aspect of the neurosphere, this work gathered methods from different field, from image processing and analysis, biomedical imaging, bioinformatics and artificial intelligence. Two modeling approaches, respectively using Delaunay mesh structure and evolution algorithm, are proposed to extract the cells configuration present in the microscope observation. Finally, the global framework allows the enhancement of neurosphere proliferation monitoring, an augmented reality support visualisation process (Fig. 2) and a tool for the extract of structural information from the different neurosphere observation. It opens new perspective for neural stem cells research, in term of observation and high-content analysis.

Author's Publication

Conference Papers

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[3] **S. U. Rigaud** and Nicolas Loménie. Neural stem cell tracking with phase contrast video microscopy. In *SPIE Medical Imaging*, pages 796230–796236, 2011.

White Papers

[4] H. Irshad, **S. U. Rigaud**, and A. Gouaillard. Primal/dual mesh with application to triangular/simplex mesh and delaunay/voronoi. *Insight Journal*, pages 1–14, 2012.

[5] **S. U. Rigaud** and A. Gouaillard. Incremental delaunay triangulation. *Insight Journal*, pages 1–5, 2012.

[6] **S. U. Rigaud** and A. Gouaillard. Walk in a triangulation : Straight walk. *Insight Journal*, pages 1–3, 2012.

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[7] **S. U. Rigaud**. Neural stem cell tracking under phase-contrast time-lapse microscopy. Master's thesis, University of Pierre and Marie Curie (Paris 6), IPAL Lab (Singapore), 2010.