

# 3D modelling and gene expression mapping in the developing human brain

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## Introduction

Characterising gene expression patterns is a crucial part of understanding the molecular determinants of development and the role of genes in disease. Although, the mouse model is a valuable system to study human developmental disorders, differences between human and mouse transcriptomes underline the importance of gene expression studies during human development (Fougerousse et al. 2000).

Human brain architecture and function are linked and defined by distinct classes of neurons and support cells. Embryonic brain development is characterised by dramatic changes in shape and size. WNT1 and FGF8 genes express key signalling components of the isthmic organiser in the brain (Wurst and Bally-Cuif 2001), and are involved in structural differentiation, patterning and organogenesis (Prakash and Wurst 2004).

## Methodology

Detection methodologies such as in situ hybridisation (ISH) and computer-based image manipulation help define the gene expression patterns underlying brain changes. A set of three-dimensional (3D) models have been generated using optical projection topography (OPT, Sharpe et al. 2002), which serve as the framework onto which expression patterns are mapped with custom designed software (MAPaint). In order to visualise and interpret developmental changes, the expression patterns of the WNT1 and FGF8 mRNAs were compared at Carnegie stage 15 (CS15; 33 days post conception).

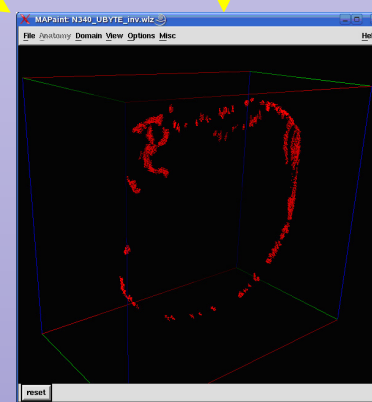
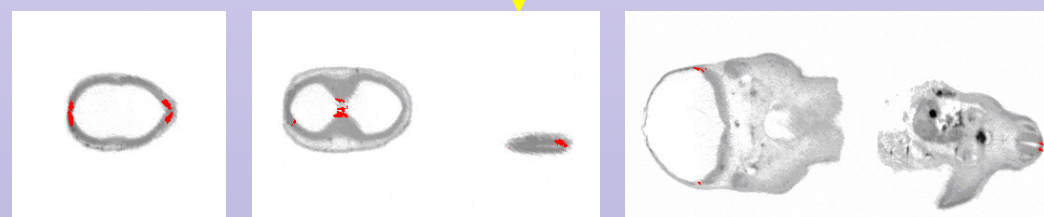
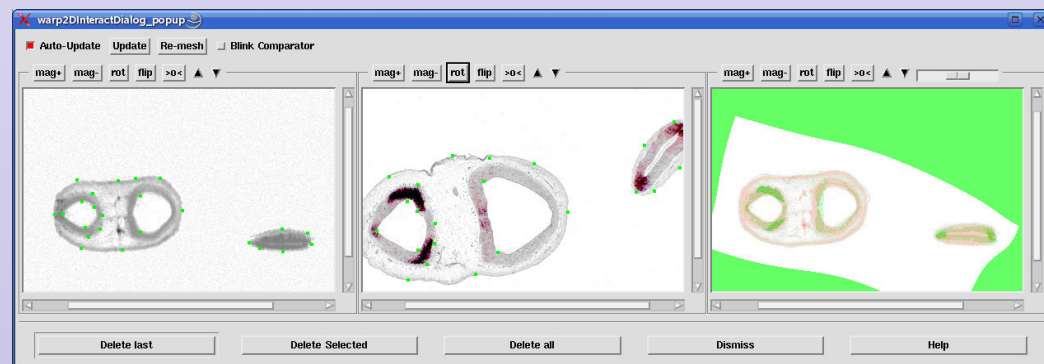


Figure 1. 3D modelling. Physical sections stained by ISH for WNT1 and FGF8 were mapped against digital sections of the CS15 OPT model. The digitised sections were warped to the OPT model section. Expression was then threshold out and mapped onto the model (shown in red).

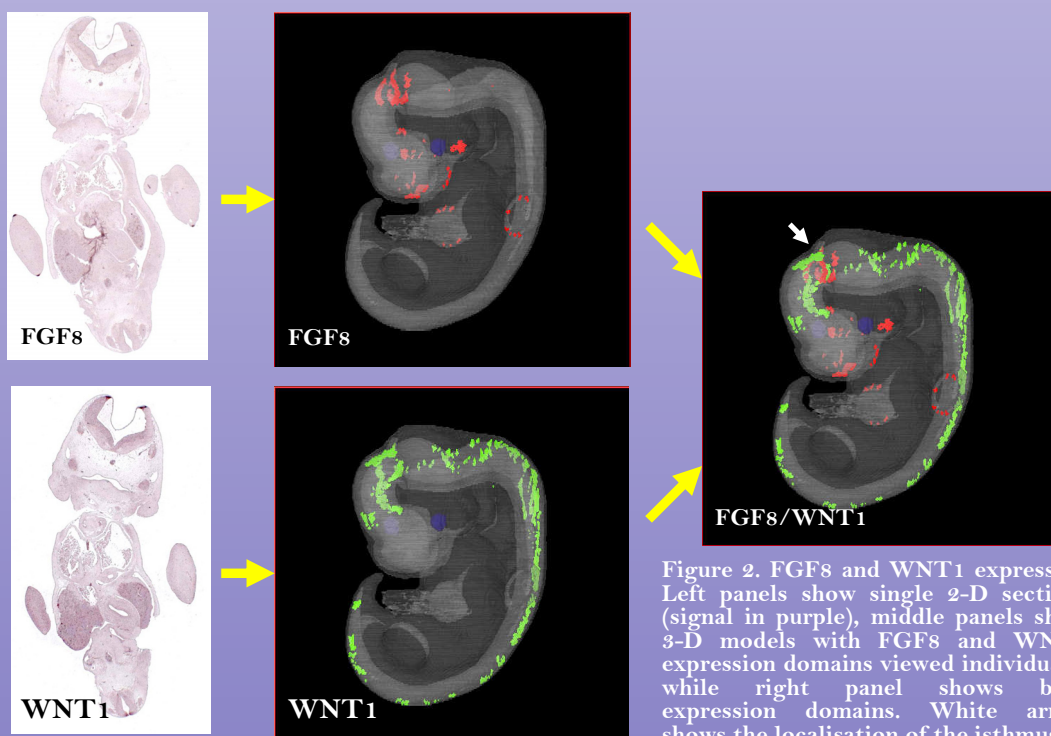


Figure 2. FGF8 and WNT1 expression. Left panels show single 2-D sections (signal in purple), middle panels show 3-D models with FGF8 and WNT1 expression domains viewed individually while right panel shows both expression domains. White arrow shows the localisation of the isthmus.

## 3D Modelling

Figure 1 presents the modelling procedure for digitised sections. The process was repeated for all available sections, then visualised for interpretation as a 3D model (shown in red, Figure 1), followed by storage.

## Outcome

WNT1 and FGF8 mRNAs were expressed in discrete regions (WNT1 in the roof plate and tegmentum; FGF8 in the hypothalamus, forebrain, optic stalks, facial processes and limbs), but also overlapped in the isthmic region. Gene expression patterns, and selected structures or boundaries, could be visualised either independently or in combination (Figure 2). While 2D images show the exact signal location, the 3D model shows the overall signal distribution. Together, these provide more complex and complete information on specific anatomical and global areas of gene expression.

## Future work

Further experiments are necessary in order to clarify the 3D co-expression at the 2D level by double-labelling ISH for the expression of the two genes at one or more Carnegie stages. The 3D modelling techniques can be applied further, in order to study gene expression during different developmental stages, or the development of other complex structures such as the heart. New insights into embryonic gene expression may be brought about by a combination of OPT, 3D modelling and magnetic resonance imaging. Education in embryology can benefit from developing a virtual reality interface using Amira software, from virtual access to these 3D models or from virtual microscopy by remote viewing, data sharing and data mining. 3D simulation of organ development may be achieved using the Reactive Animation concept and 3D models of a set of genes in a series of all stages of human development from CS 12 (26 days post conception) to CS23 (56 days post conception).

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