A visual analytics technique for exploring gene expression in the developing mouse embryo

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A Visual Analytics Technique for Exploring Gene Expression in the Developing Mouse Embryo

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Abstract. This paper describes a novel visual analytics technique for exploring gene expression in the developing mouse embryo. The majority of existing techniques either visualise a single gene profile or a single tissue profile, whereas the technique presented here combines both - visualising the genes expressed in each tissue in a group of tissues (the components of the developing heart, for example). The technique is presented using data, provided by the Edinburgh Mouse Atlas Project, of gene expression assays conducted on tissues of the developing mouse embryo and a corresponding hierarchical graph of tissues defining the mouse anatomy. By specifying a particular tissue, such as the heart, and a particular stage of development, a Formal Context is computed making use of the hierarchical mouse anatomy so that the resulting Formal Concept Lattice visualises the components of the specified tissue and the genes expressed in each component. An algorithm is presented that defines the computation of the Formal Context. Examples of resulting lattices are given to illustrate the technique and show how it can provide useful information to researchers of gene expression and embryo development.

1 Introduction

Understanding the role of genes in the development of an embryo is a major scientific endeavour. Key advances such as the mapping of the human genome[3], the identification of specific genes responsible for genetic diseases [1] and the latest gene splicing technologies, such as the CRISPR-cas9 system [2], have led to new methods and treatments for the detection, prevention and correction of many genetic disorders [3]. However, there is still much to be done to gain a complete picture of how the many thousands of genes present in complex organisms are responsible for the construction, differentiation and organisation of the

[3] https://www.genome.gov/

many different cells that constitute the organism. By studying the components of a developing embryo, in terms of finding out which genes are responsible for constructing which systems, organs and tissues therein, a fuller picture is emerging.

One major effort in this regard is the e-Mouse Atlas Project [4, 5] where in situ gene expression experiments for the embryonic mouse are aggregated and published. Data is being collected that identifies which, of over 6000 genes, are responsible for the construction of over 4000 different tissues in the developing mouse embryo.

This paper presents a new visual analytics technique to explore this data, allowing the visualisation of the genes expressed in a specified mouse embryo tissue and all of its component parts (such as the heart and its components, comprising atria, ventricles, valves, etc.). The visualisation also enables gene co-expression to be seen, where groups of genes are expressed together in the same tissue.

For this purpose Formal Concept Analysis (FCA) [6] is used to create the visualisation in the form of a Formal Concept Lattice. Whereas the majority of existing techniques tend to focus on either a single gene profile across different tissues, or single tissue profile of genes expressed therein, the Formal Concept Lattice of gene expression combines both in a single diagram (for those not familiar with FCA, these are good introductory texts: [7, 8]).

The structure of the rest of this paper is as follows: Section 2 describes the e-Mouse Atlas Project (EMAP), Section 3 shows how the EMAP data and a corresponding definition of the mouse anatomy can be used to create a Formal Context of gene expression, Section 4 evaluates the results by means of a number of Formal Concept Lattices of gene expression, Section 5 is a review of existing techniques and other related work and Section 6 draws conclusions from the work and suggests further work to be done.

2 The e-Mouse Atlas Project

The e-Mouse Atlas Project (EMAP) provides researchers with two main resources: the EMA Mouse Anatomy Atlas and the EMAGE Gene Expression Database [9].

The EMA Mouse Anatomy Atlas uses embryological mouse models to provide a digital atlas of mouse development. It is based on the definitive books of mouse embryonic development by Theiler [10] and Kaufman [11] yet extends these studies by creating a series of three dimensional computer models of mouse embryos at successive stages of development with defined anatomical domains linked by a stage-by-stage ontology of anatomical tissue names.

The stages of mouse embryonic development in the EMA Mouse Anatomy Atlas are based on those defined by Theiler [10]. Theiler defined 26 stages of embryonic development, from Theiler Stage 1: *the one-cell egg* to Theiler Stage 26: *Long Whiskers*. In EMAP, each Theiler Stage is represented in an anatomical ontology (from Kaufman [11]) and a corresponding three dimensional computer

model. Figure 1 shows part of the anatomy ontology at Theiler Stage 13, where *cardiovascular system* and *heart* have been expanded to show their component parts. Each anatomical term is annotated with a unique ID (EMAPA number) and the Theiler Stages in which it is present. Note that, although Figure 1 resembles a taxonomy, it is actually an ontology: a parent tissue can have several child tissues but also a child tissue can have more than one parent.

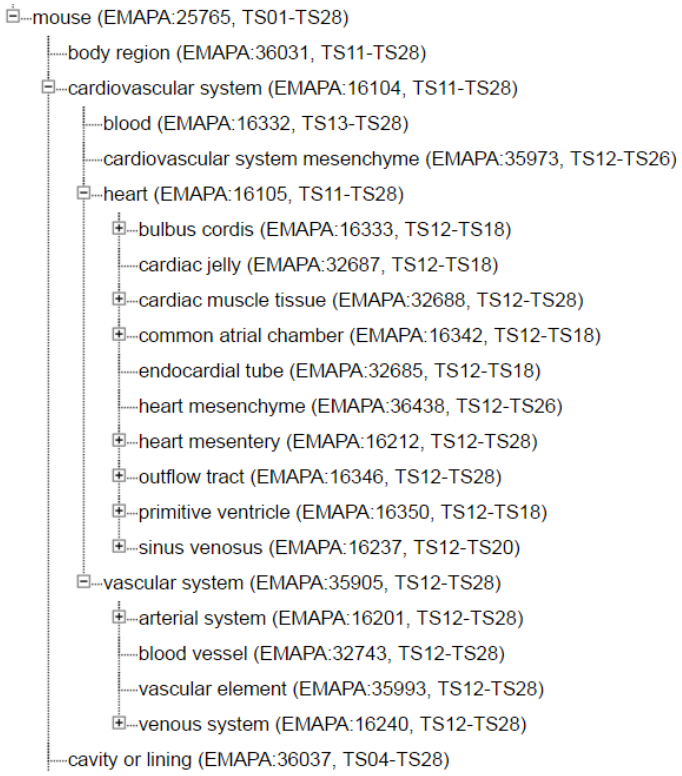


Fig. 1: Part of the anatomy ontology for Theiler Stage 13. Source: [5].

EMAGE is a database of *in situ* gene expression data in the mouse embryo and an accompanying suite of tools to search and analyse the data. The majority of the data is based on whole-mount (whole embryo) and embryo section assays. The embryo or section is stained-up for a particular gene of interest to show where the gene is being expressed. The scientist carrying out the assay has to determine in which tissues the gene is being expressed and how strongly it is expressed by the level of staining. The strength of expression in a tissue is denoted as one of a number of possible values: *detected*, *not detected*, *possible*, *strong*, *moderate* or *weak*. Table 1 is a representation of EMAGE data, with

values for Theiler Stage, *emageID* (a unique assay number) , *gene*, *strength*, *tissueName* and *emapaId* (a unique tissue ID). Note that several tissues can be examined in the same assay and, that for the purposes of data analysis, all components of the embryo are called tissues, including organs, systems and even the mouse itself.

stage	emageID	gene	strength	tissueName	emapaId
17	503	Mfng	detected	cranial ganglion	16659
17	503	Mfng	detected	hindlimb ridge	16593
17	504	Actc1	strong	dorsal aorta	16204
17	504	Actc1	strong	branchial arch	16117
15	505	Zeb1	detected	branchial arch	16117
15	505	Zeb1	detected	cranial ganglion	16659
15	505	Zeb1	strong	hindlimb ridge	16593

Table 1: A representation of EMAGE data.

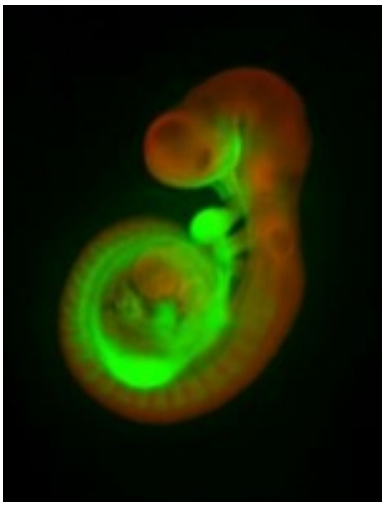
Figure 2 shows an example of a whole-mount assay and the resulting spatial annotation for gene Gpc3 at Theiler Stage 15: The results of the whole-mount assay (a) are mapped onto a corresponding 2D section of the model (b) using a colour-coding to indicate the strength of expression. However, this type of visualisation is not particularly useful if we wish to show *all* the genes expressed in a group of tissues. To do this, one possibility is to use Formal Concept Analysis, taking genes to be formal objects and tissues to be formal attributes. This technique is described in the next Section.

3 Creating a Formal Context of Gene Expression

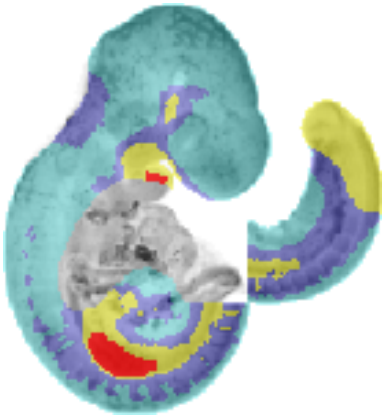
A formal context of gene expression can be created from EMAGE data taking genes to be formal objects and tissues to be formal attributes. If gene g is detected in tissue t, for example, the relation (g, t) is added to the context. Of course, this approach loses the detail of strength of expression and is useful only if we are interested in whether a gene has been detected or not. In which case, the strengths *weak*, *moderated* and *strong* can all be taken to imply *detected*.

Taking the EMAGE data in Table 1 as an example, a corresponding formal context is shown in Figure 3(a) and the resulting concept lattice in Figure 3(b)[4]. Thus gene *Actc1* is expressed in the *dorsal aorta* and the *branchial arch*, *Zeb1* is expressed in the *branchial arch*, the *hindlimb ridge* and the *cranial ganglion*, and *Mfng* is expressed in the *hindlimb ridge* and the *cranial ganglion*.

[4] The lattices presented in this paper were all produced using Concept Explorer [12] available at `https://sourceforge.net/projects/conexp/`



(a) Whole-mount assay

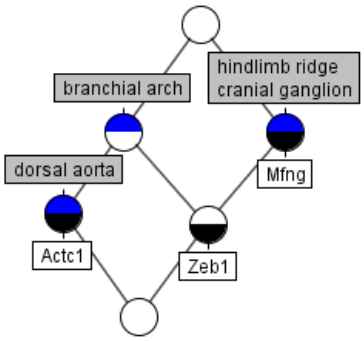


(b) 2D Spatial Annotation

Fig. 2: Whole mount assay and spatial annotation of gene Gpc3 at TS15. Name: EMAGE 3837. Source: [9].

	cranial ganglion	hindlimb ridge	dorsal aorta	branchial arch
Mfng	×	×		
Actc1			×	×
Zeb1	×	×		×

(a)



(b)

Fig. 3: Formal context and resulting lattice derived from the EMAGE data extract in Table 1.

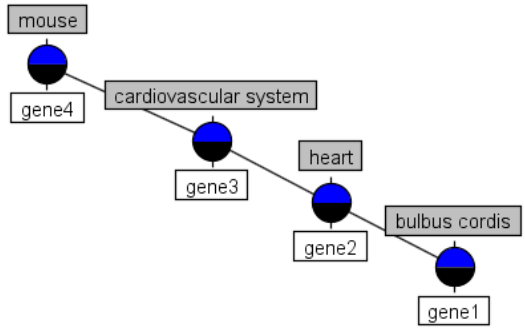
3.1 Inferred gene expression results

The hierarchical nature of the mouse anatomy ontology means that additional results can be inferred from an assay. If a gene is detected in a tissue then, by definition, it is also expressed in that tissue's parent tissue, and so on up the anatomy. Taking the part anatomy shown in Figure 1 as an example, if a gene is detected in the *bulbus cordis* then it can be inferred that the gene is expressed in the *heart*, the *cardiovascular system* and the *mouse*. This is known as *positive propagation* of gene expression.

This positive propagation is useful to FCA in producing a gene expression visualisation that corresponds to the hierarchy in the mouse anatomy ontology. For example, in a number of assays let us say that *gene1* was detected in the *bulbus cordis*, *gene2* was detected in the *heart*, *gene3* was detected in the *cardiovascular system* and *gene4* was detected in the *mouse*. The corresponding formal context is shown in Figure 4a and the resulting lattice in Figure 4b. The lattice clearly visualises the hierarchy of the mouse anatomy ontology thus providing a familiar and sensible structure for researchers to analyse.

	mouse	cardiovascular system	heart	bulbus cordis
gene1	×	×	×	×
gene2	×	×	×	
gene3	×	×		
gene4	×			

(a)



(b)

Fig. 4: Formal context and resulting lattice demonstrating positive propagation of gene expression.

3.2 An algorithm for creating formal contexts of gene expression from EMAGE data

Although it is possible to create a formal context from all of the data the EMAGE database, the resulting concept lattice would be far to large to analyse. Instead,

what is proposed here is to create a formal context of gene expression for a particular tissue of interest (such as an organ or system) and all of its component parts at a given Theiler Stage. The algorithm, *FindDetectedGenesInTissue*, presented below, automates the construction of such formal contexts.

The algorithm is invoked by passing it the tissue and Theiler Stage of interest and an initially empty set of tissues called $family\_line$. This set of tissues is used to store (in line 2 of the algorithm) an ancestral line of tissues from the initial tissue of interest, to a child of that tissue, a grandchild and so on. This family line of tissues provides the means of carrying out positive propagation of gene expression.

In line 3 of the algorithm, the EMAGE database is searched to find results involving the tissue and Theiler Stage of interest. For each such result, if the strength of the result is *detected*, *strong*, *moderate* or *weak*, then, in line 6 and 7, for each tissue in the current family line, a relation between each tissue and the gene in the result is added to the formal context being created, thus carrying out positive propagation of the gene's expression.

The algorithm is then recursive, passing to itself successively each child of the current tissue along with the original Theiler Stage and the current family line of tissues. The mouse anatomy for each Theiler Stage is stored as a data set of $(childtissue, parenttissue)$ pairs. Thus is it simply a case of searching for each instance of a parent tissue to enumerate its children.

FindDetectedGenesInTissue$(tissue, tstage, family\_line)$

```
1  begin
2      family_line ← family_line ∪ {tissue}
3      foreach result in EMAGEdatabase do
4          if result.tissueName = tissue and result.stage = tstage and
           (result.strength = "detected" or result.strength = "strong" or
           result.strength = "moderate" or result.strength = "weak") then
5              remark positive propagation of gene expression:
6              foreach Tissue in family_line do
7                  context ← context ∪ {(result.gene, Tissue)}
8      foreach child of tissue in MouseAnatomy(tstage) do
9          FindDetectedGenesInTissue (child, tstage, family_line)
10 end
```

4 Concept Lattices of Gene Expression

The *FindDetectedGenesInTissue* algorithm was implemented in C++ and a series of gene expression analyses were carried out. The first analysis is of the *eye*

and its components at Theiler Stage 16 and the second analysis of the development of the *heart atrium* over a number of Theiler Stages.

Figure 5 is a lattice showing gene expression in the *eye* at Theiler Stage 16. The genes expressed in the eye and its various components are clearly seen. In some cases, such as the *optic cup*, there appears quite a large number of co-expressed genes. This may indicate that the tissue is composed of many different proteins or may be an example of several genes working together to produce a single protein - sometimes one or more 'enabler' genes are required for the expression of the protein making gene [13]: the products of two genes, for example, (called *transcription factors*) work together to influence the expression of another gene and therefore the amount of protein product of that gene.

Other, more specialised tissues, such as the *optic cup intraretinal space*, show the expression of a single gene, which may indicate that the tissue is predominantly composed of a single protein. There are also interesting cases of genes, such as *Cdh2*, that are expressed in two or more unrelated tissues (tissues that are not in the same branch in the anatomy ontology), in this case the *optic cup* and the *lens pit*. This may indicate that, although not directly related, the tissues share some similarity in function or structure. It is also interesting to look at gene expression in tissues that clearly, from their names, have some commonality and often share the same parent tissue, such as the *optic cup outer layer* and the *optic cup inner layer*. Here we can see that gene *Wnt2b* is expressed in both layers, but also that each layer has genes specific to it. The shared gene may be responsible for a common function or structure whilst the specific genes may be responsible for the structural or functional differences between the tissues.

Figures 6 and 7 show lattices of gene expression in the *heart atrium* across four Theiler Stages: 14 (Figure 6(a)), 15 (Figure 6(b)), 16 (Figure 7(a)) and 17 (Figure 7(b)). The lattices clearly show changes in gene expression during the development of the *heart atrium* over these Stages. In the earliest Stage, there are only four components and three genes. The atrium at this stage consists primarily of *cardiac muscle* being constructed by two genes, *Vcam1* and *Myly*. The other gene, *Nppa*, continues to be expressed in the *heart atrium* through Stages 15 and 16. Its early presence and the subsequent proliferation of genes expressed with it in the *heart atrium* in TS 15 may suggest that it has a role as controlling gene or *core transcription factor* [14, 15], responsible for the activation of other genes during the *heart atrium* development. TS 15 introduces the *common atrial chamber endocardial lining* with two genes being expressed therein. The two *cardiac muscle* genes, *Vcam1* and *Myl7*, in TS 14 are now replaced in TS 15 by five new genes. It is interesting to note that gene *Myl7* seems to have moved from the *cardiac muscle* up to the *heart*. It must be noted, however, that the EMAGE database is not yet complete and this may be a case where *Myl7* has not been assayed in the *cardiac muscle* at TS 15. If, however, it has and was found not to be detected, then this would represent an unusual and interesting finding. In TS 16 the *common atrial chamber* divides into two parts, *left* and *right*, and the gene *Pitx2*, having appeared in the *heart atrium* in TS 14, now moves down to the *common atrial chamber left part*, adding to the suggestion

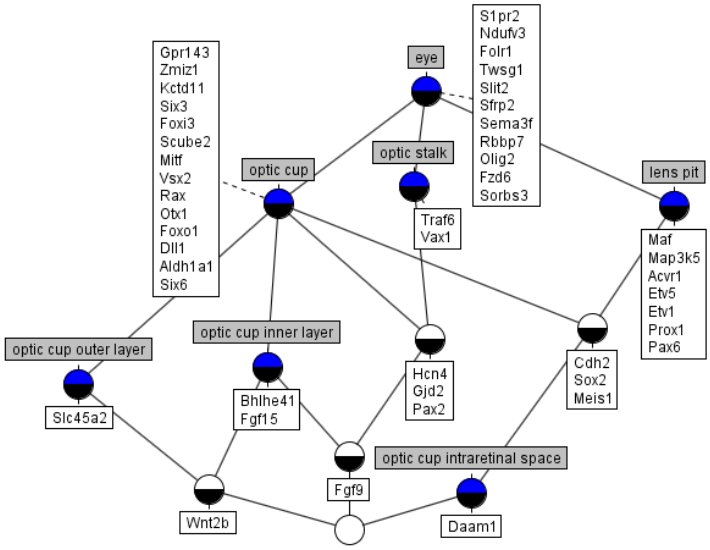
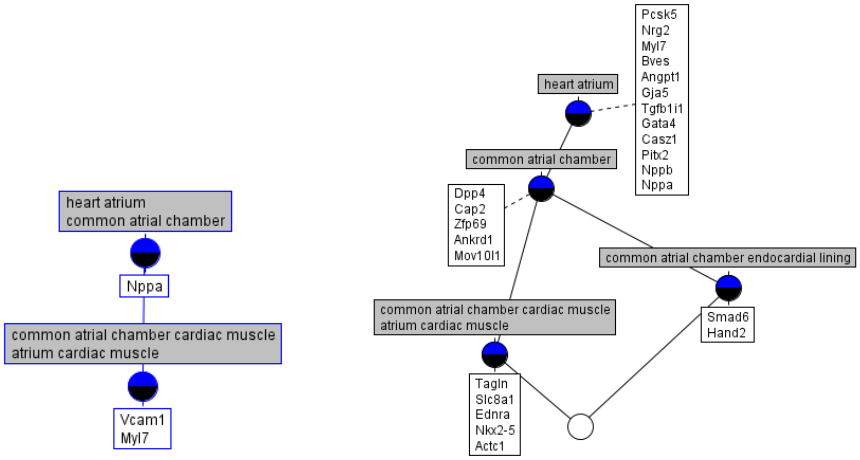


Fig. 5: Lattice of gene expression in the *eye* at Theiler Stage 16.

that it was activated in TS 15 (perhaps by *Nppa*) and is now being expressed in the specific tissue for which it is responsible. In the course of development, an early, undifferentiated tissue will have many genes activated within it that are then responsible for the development of the subsequent components of that tissue. The *cardiac muscles* fail to appear in the TS 16 lattice but then reappear in the TS 17 lattice. Clearly they do not physically disappear and then reappear, so again this may be a case where the data is incomplete. It is also striking by how much gene expression changes over a small time-frame of development and in the same tissues. In fact, very few of the genes in the *heart atrium* lattices appear more than once and often the genes expressed in a particular tissue at one Theiler Stage are replaced by a completely different set of genes in the next Theiler Stage. At the moment, how much of this is due to rapid changes in tissue development and how much is due to missing data, is not known.

The results were also evaluated by a biologist working on the EMAP. The biologist liked the smaller lattices (such as those presented here) but found larger lattices hard to read (the lattice for the brain at TS 18 has 25 nodes and 137 genes, for example). The biologist suggested that a 'dynamic' visualisation might be useful, allowing the user to "walk through the nodes". Whilst this is not possible using Concept Explorer, an implementation of expandable formal concept trees is, however, available that would provide this feature [16]. Being able to compare gene expression over a number of Theiler Stages was also found to be useful, but the incompleteness of the data set is currently proving to be a barrier to producing a full picture.



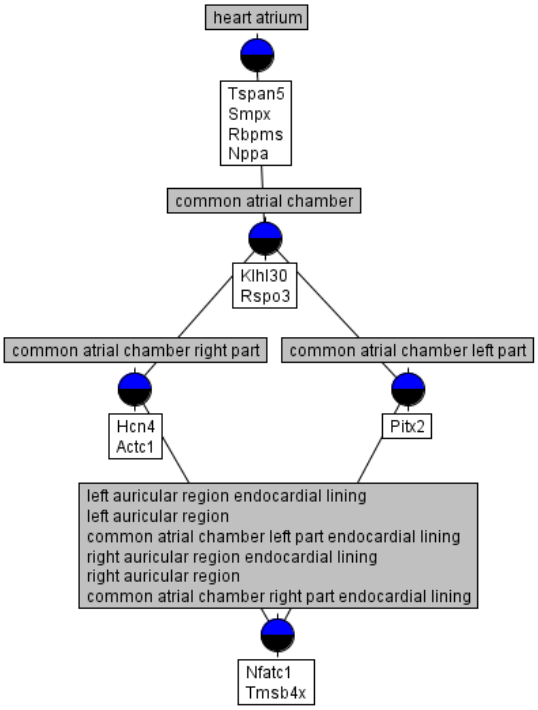
(a) TS 14 (b) TS 15

Fig. 6: Lattices of gene expression in the *heart atrium* across Theiler Stages 14 and 15.

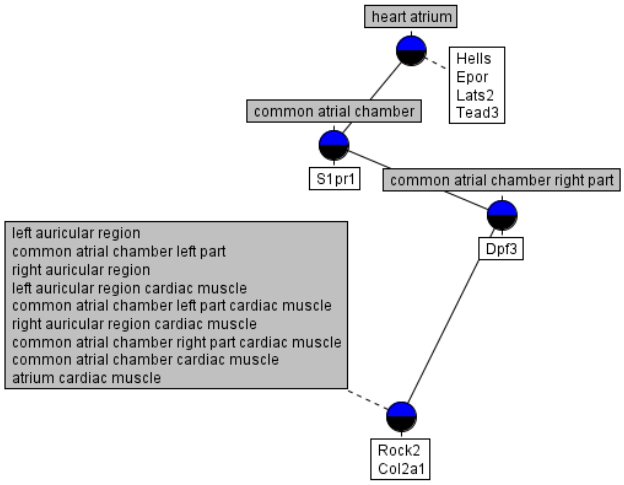
5 Related Work

The work presented here builds on research carried out in the European CUBIST Project [17], where novel FCA-based analytics were being developed for a number of use-cases, one of which was the EMAP. One strand of CUBIST developed a technique for identifying large gene co-expressions, typically at the system level (e.g., in the skeletal system) [18]. Thus, for example, the work was able to identify all the genes involved with the construction of the skeletal system. Because of the large amount of missing data in EMAGE (simply due to the large number of genes and tissues involved) this technique employed an element of FCA 'fault tolerance' [19] to predict possible gene expressions at the system level.

Other related work in CUBIST included an investigation of alternative visualisations to the concept lattice [20]. Following this investigation, [21] explored the use of sunburst diagrams to visualise individual gene profiles. Another strand of CUBIST involved the development of an RDF version of the EMAGE database and mouse anatomy ontology, along with novel gene expressions queries made possible via the SPARQL query language [22]. The prototype query tool developed comes closest to the work presented here, in that SPARQL queries may be possible that perform the same task as *FindDetectedGenesInTissue*. In any case, the mouse anatomy ontology used in the work has since been superseded by the current one in EMAP, which would require a re-construction of the RDF model and data to replicate the work. Useful results were obtained, however, in using SPARQL queries to find contradictory results in the EMAGE data, e.g., where one result for a particular gene in a particular tissue at a particular Theiler Stage



(a) TS 16



(b) TS 17

Fig. 7: Lattices of gene expression in the *heart atrium* across Theiler Stages 16 and 17.

says *detected* but another result with the same gene, same tissue (or a tissue that the first tissue is a part of) and same Theiler Stage says *not detected*.

FCA appears to be attractive in the study of gene co-expression because formal concepts are natural representations of maximal groups of co-expressed genes. For example, in [23] FCA was used to extract groups of genes with similar expressions profiles from data of the fungus *Laccaria bicolor* and in [24] human SAGE data provided the example from which clusters of genes with similar properties are visualised. In both approaches the complexity, in terms of the large number of formal concepts present in the raw data, was managed by specifying a concept's minimum size (the well known idea of minimum support in FCA and frequent itemset mining). In [24], tools were developed to query the set of extracted concepts according to various criteria (e.g., presence of a keyword in a gene description) and then to cluster concepts according to similarity, in terms of the attributes (samples) and objects (genes above a threshold of expression) in them. They called these clusters *quasi-synexpression-groups* (QSGs). By contrast, in [25, 26], ranges of a measure of gene concentration were used as attributes and the genes as objects. Individual concepts that satisfied a specified minimum size were then examined by, for example, plotting the actual measures of concentration of genes together in a line plot.

Of course, non-FCA based visualisations of gene expression have also been used by researchers. A notable example is the heatmap, often used to visualise the results of micro-array gene expression profiling [27]. This is a technique for simultaneously measuring the expression levels of thousands of genes for a single sample on one micro-array chip. The micro-array technique is often used in clinical research where a sample of the same tissue is taken from each patient in the study and each sample placed in its own micro-array chip. In order to visualize the micro-array data of different samples, a colour-coded heatmap is generally used, along with a clustering algorithm, allowing the gene profiles to be compared. Figure 8 is such an example where each row is a cancer tumour sample and each column is a gene [28].

6 Conclusions and Further Work

This paper has demonstrated that FCA can provide a useful and novel visualisation of gene expression that combines gene and tissue profiles (i.e., allows both genes and tissues to be displayed together in a single graph. An algorithm called *FindDetectedGenesInTissue* has been developed that incorporates a defined mouse anatomy taxonomy to interrogate the EMAGE database of gene expression for all components of a specified tissue of interest. The algorithm also incorporates positive gene expression propagation to produce a natural hierarchical visualisation of gene expression based on the defined mouse anatomy ontology.

It has been less easy to demonstrate the full potential of comparing gene expression over a series of Theiler Stages of embryo development, due to the large quantify of missing data. The database is far from complete, with many

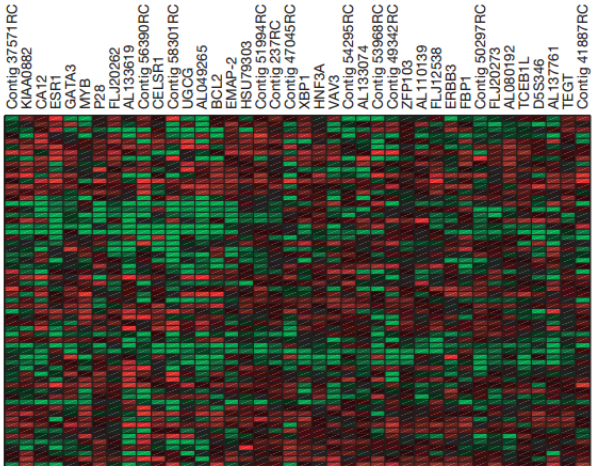


Fig. 8: Example of a heat-map of gene expression in cancer tumours. Source: [28].

assays still to be conducted, but once the database is complete, analyses across Theiler Stages should be more fruitful. Indeed it may be useful to develop a sort of 'Theiler Stage algebra' whereby, for a specific tissue of interest, one Theiler Stage (formal context) can be subtracted from another, for example, to determine the expressions present in the first Stage but not the second. Alternatively, the intersection of two or more Stages could be carried out to determine the expressions that remain constant over that time.

Although researchers are usually interested in where genes are expressed, they are sometimes interested in finding out where genes are *not* expressed. The EMAGE database already records these *not detected* results and it would be a simple task to modify the algorithm and software to carry out the query. However, the incorporation of positive gene expression propagation would need to be replaced by its corollary, *negative propagation*. In this case, if a gene is not detected in a particular tissue, then it can be inferred that it is also not expressed in all the components of that tissue. The algorithm would thus have to be modified accordingly.

Given a complete EMAGE database, a tool can thus be envisaged that includes the *not detected* query along with a simple set of Theiler Stage algebra and a simple user interface that would provide the researcher a useful technique for gene expression analysis of mouse embryo development.

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