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Progress with a Multiscale Systems Engineering Approach to Cardiac Development

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Multiscale systems engineering provides a way to integrate models of real-world phenomena that allows a holistic understanding of component interactions at different levels of scale simultaneously. The discipline draws upon information engineering to provide ontological representations that are derived from digital libraries of terms, themselves found at distributed locations around the world. Cardiac development is well understood within discrete levels of analysis. The application of the multiscale framework gives added value by unlocking the relationships between genetic-based information at one level of analysis and the phenotype it encodes for at the cell and organ levels of abstraction. The multiscale-based relationships have begun to demonstrate new insights into normal cardiac development and conditions that give rise to congenital heart diseases such as the tetralogy of Fallot. This paper describes progress made in combining ontology-based information models and explains the importance of the role of multiscale systems engineering.

Key words: Cardiac development, Information engineering, Multiscale, Ontology

Napredak koncepta višerazinskog sustavskog inženjerstva u razumijevanju srčanog razvoja. Višerazinsko sustavsko inženjerstvo pruža mogućnost integracije modela različitih pojava iz stvarnog svijeta, što omogućuje cjelovito razumijevanje interakcija komponenti sustava istovremeno na različitim razinama skale. Disciplina je to koja koristi informatiku za omogućavanje ontoloških reprezentacija koje se izvode iz digitalnih knjižnica pojmova smještenih na raspodijeljnim lokacijama širom svijeta. Unutar pojedinačnih razina analize postoji dobro razmijevanje srčanog razvoja. Primjena višerazinskog okvira daje dodatnu vrijednost otključavajući vezu između genetski temeljenih informacija na jednoj razini analize i fenotipa koji kodira na razinama apstrakcije stanice i organa. Višerazinski temeljene veze počele su donositi nove spoznaje normalnog srčanog razvoja i uvjeta koji vode k pojavi prirođenih srčanih grešaka kao što je Fallotova tetralogija. Ovaj rad opisuje napredak postignut kombiniranjem ontologijski temeljenih infomacijskih modela i objašnjava važnost uloge višerazinskog sustavskog inženjerstva.

Ključne riječi: srčani razvoj, informatika, višerazinski pristup, ontologija

1 INTRODUCTION

Multiscale systems engineering can be defined as the field of understanding physical systems that possess measurable characteristics at multiple scales. Although these characteristics can be exhibited in multiple spatial or time scales, only the former is considered in this paper. The multiscale approach to be demonstrated also owes much to methods derived from other domains, including those from systems engineering (e.g. integration technologies and information modelling); the Physiome project [1] (which has many multiscale-based physiological models documented and archived at a web-site managed by the University of Auckland, New Zealand, and the University of Washington, USA [e.g. 2]); and the EU-funded Network of Excellence on the Virtual Physiological Human (VPH) [3]. Physiome/VPH researchers collaborate to provide curated, interoperable model repositories of biophysical mechanisms and their underpinning biochemical reaction networks that are able to be re-used in whole or in part. Scale-linking is a key challenge in multiscale systems engineering. This can be achieved in various ways. Efforts elsewhere focus on a mathematical approach, while here we demonstrate scale-linking via information engineering through the use of multiple ontologies.

The interoperable nature of the system is a consequence of the use of recognised mark-up language standards, notably the Systems Biology Mark-up Language (SBML) principally for the biochemistry based components [4] and the Cell Mark-up Language (CellML) for the biophysics components [5]. In parallel, members of the Open Biomedical Ontologies (OBO) Foundry initiative [6] are developing a suite of reference information models that can

be used for annotating a wide variety of biomedical knowledge sources. These sources include images (regions of which can be annotated by segmentation), database entries, publications, computational models and simulation results. OBO Foundry-based ontologies also provide increasingly good coverage of biomedical concepts at different levels of spatial and temporal scale, and provide a structure that avoids logical inconsistencies which were an issue in previous work. The need to annotate phenotypic data has led to a post-composition approach in which terms from reference ontologies are combined to form terms of greater specificity. This is explained in Section 3, and applied to cardiac development in Section 4.

Physiome modelling efforts have tended to focus on the physiology of adult organ systems, such as the heart [7] or lungs [8]. The work reported here represents a multidisciplinary and international collaboration between clinicians, biomedical systems engineers and information engineering specialists in Rennes, Paris (both France) and Loughborough (UK). The team is tailoring the multiscale framework for application to morphogenesis of the human embryonic heart. The aim of this work is to illustrate the mechanisms by which congenital heart defects arise by providing validated multiscale models of morphogenetic processes. Many genetic factors have been identified; however, what is unknown are the mechanisms by which altered genetic, protein and cell signalling pathways lead to specific abnormal cardiac development. The initial use cases are focused on protein interactions with the cell level of scale, where existing curated models may be leveraged. The outputs of these models will be correlated to phenotypic data of higher level morphology, including images of a particular congenital heart defect known as the tetralogy of Fallot.

2 CLINICAL ASPECTS

The development of the embryonic heart commences in week 2 of gestation and is fully formed by week 8. This process is well documented [e.g. 9]. Week 2 of foetal life provides the first milestone of cardiac development when the two endocardial tubes that form the primitive heart join together. At this stage of development the first cardiac muscle contractions occur, giving rise to both blood circulation and electrophysiological signals that form a primitive electrocardiogram [10]. At the end of week 3 the heart tube folds into an S-shape, looping to the right. This repositioning constitutes a crucial step towards the morphology of the heart because it brings the future heart chambers and their inflow and outflow tracts into their relative spatial positions. Throughout week 4 the ventricles grow considerably, in particular the right ventricle, and at the same time the ventricular septum forms dividing the ventricles. During this time, the embryo grows from 4 mm to around 50 mm in length.

Two processes in the development of the embryonic heart are important in the understanding of congenital heart diseases: looping and aortic wedging. Looping is the first manifestation of asymmetry in the embryo that continues into adult life. Aortic wedging occurs as a consequence of rotation of the myocardial wall of the Outflow Tract (OFT), itself secondary to the re-modeling of the inner curvature of the heart (see Fig. 1).

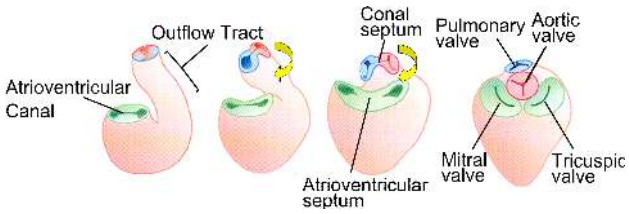

Fig. 1. Heart looping and wedging. After [9].

This rotation leads to the development of the aortic valve. Initially it is located on the right-hand side of the OFT. It takes its final resting place nestled between the mitral and tricuspid valves. When the heart is fully formed at 8 weeks, the aorta is posterior to the pulmonary artery, with the degree of rotation about 30 degrees short of a complete juxtaposition of 180 degrees. At the same time, the conal and atrioventricular septa develop by fusion of the endocardial cushions. These cushions are swellings which occur in the OFT and the AVC as a result of endocardial cells losing their cohesion and invading the extracellular matrix; a process termed epithelial to mesenchymal transformation (EMT). Slight differences in the degree rotation and EMT can lead to congenital heart defects.

The difference between types of congenital heart disease can be extremely close and have the same underlying cause. The tetralogy of Fallot (TOF) is defined as the association of four anatomic features: overriding aorta (less to the left than it should be), pulmonary stenosis, ventricular septal defect, and right ventricle hypertrophy. The pulmonary stenosis is caused by the malalignment and anterior deviation of the conal septum, itself resulting from a hampered wedging, leading the aorta to retain its initial rightward position. This malalignment between the conal septum and the primitive ventricular septum leads obligatorily to a ventricular septal defect. Right ventricle hypertrophy is acquired post-natally as a consequence of the pulmonary obstruction. OFT defects include transposition of the great arteries, due to a disruption of pathways that control left-to-right signaling. OFT defects include DORV, common arterial trunk and TOF [14]. As can be seen from Fig. 2 the TOF overlaps in position with DORV, with variation between 90 and 140 degrees of rotation of the OFT.

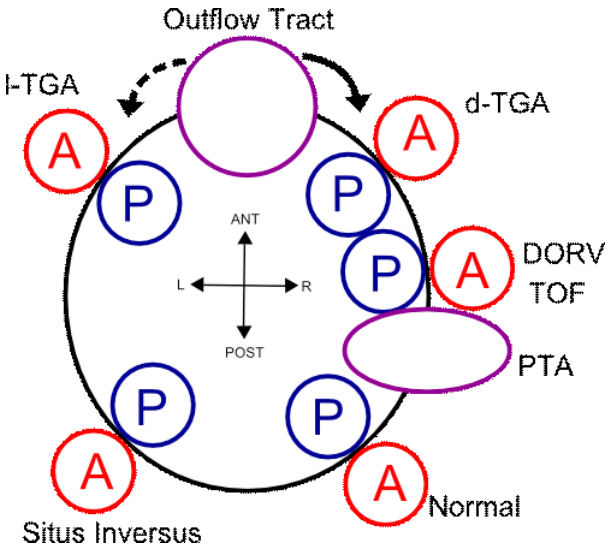

Fig. 2. Modifed Van Praagh diagram, after [13], showing the approximate rotation of the OFT corresponding to different types of Congenital Heart Defect (CHD). In PTA, there is no septation into the aorta (A) and pulmonary artery (P). DORV and TOF correspond to about 90 degrees rotation, while the rotation is approximately 150 degrees in normal development. Situs inversus is a condition where organs develop on the opposite side of the body, and hence the OFT rotates counter-clockwise rather than clockwise. This also occurs in l-TGA. Key: PTA: Persistent Truncus Arteriosus, DORV: Double Outlet Right Ventricle, l-TGA: levo-Transposition of the Great Arteries, d-TGA: dextro-Transposition of the Great Arteries, TOF: tetralogy of Fallot

3 INFORMATION ENGINEERING ASPECTS

In biomedical engineering, a wide variety of measurements are taken at different levels of scale. This gives rise to both clinical data and the results of biochemical, biophysical and physiological investigations. At the molecular level, gene expression analysis produces information on the cellular and tissue locations of gene products. At the cellular level, measurements generate data on variables such as cell volume, metabolism and electrophysiology. There are imaging techniques, applicable to different levels of granularity; such as Magnetic Resonance Imaging and Computed Tomography that can be compared with images from the Scanning Electron Microscope, gene expression maps and gel electrophoresis. An increasing amount of these biomedical data are being made available via web accessible databases. However, this can lead to a data silo issue where it is increasingly difficult to uncover relevant information from the ever increasing complexity of interdependent data sources. To accommodate this complexity, the coordination and simultaneous querying of heterogeneous databases is made possible by the adoption of common information models (ontologies). It would be impossible to define all necessary concepts for biomedicine in one ontology, and thus there is coordination between a collection of reference ontologies provided by the OBO foundry. For example, the Foundational Model of Anatomy (FMA) deals with mammalian anatomical entities, and the Cell Type (CL) deals with the classification of cell types, for all species. The most successful examples of data integration have been with the Gene Ontology (GO). Despite the name, GO is not a classification of genes or gene products. Rather, the aim of GO is to provide a standard classification for the characteristics of gene products. This means it contains information from multiple levels of scale, because, when annotating gene products, the interest lies in recording their cellular and subcellular locations, their functions as molecules (they can act as enzymes, transporters or receptors) and the biological processes that they have been associated with (at any level of scale). Thus for operational reasons GO is split into three separate ontologies: Molecular Function (GO-MF), Biological Process (GO-BP) and Cellular Component (GO-CC), as shown in Fig. 3. The actual classification of proteins is the domain of the Protein Ontology (PRO).

The Basic Formal Ontology (BFO) is an ontology, which makes only the most basic distinctions between types of entities in OBO foundry ontologies. The three ontological branches of GO fit exactly into the three most fundamental categories of the BFO. These are termed the occurents (processes that unfold through time) and continuants (entities that exist in full through a period of time). Continuants are further divided into independent continuants (physical things) and dependent continuants (qualities that physical things may have). GO-BP deals with occurents, GO-MF deals with dependent continuants at the molecular level, and GO-CC deals with cellular and subcellular independent continuants.

Two different, but complementary, approaches are emerging in phenotype classification. The Mammalian Phenotype (MP) ontology provides a robust phenotype terminology, which covers spatial scales from cellular to organism phenotypes. This has proved especially useful in providing a manageable means to annotate the rat and mouse genome databases [15]. While MP covers many scales, the degree of granularity is not sufficient for many types of phenotypic data, which are often highly descriptive and specific. The Phenotype and Trait Ontology (PATO) offers a different approach by classifying only fundamental qualities (e.g. ‘trabecular’, ‘decreased thickness’), without attempting to predefine full phenotypic descriptions. It is then left to the model curators to compose

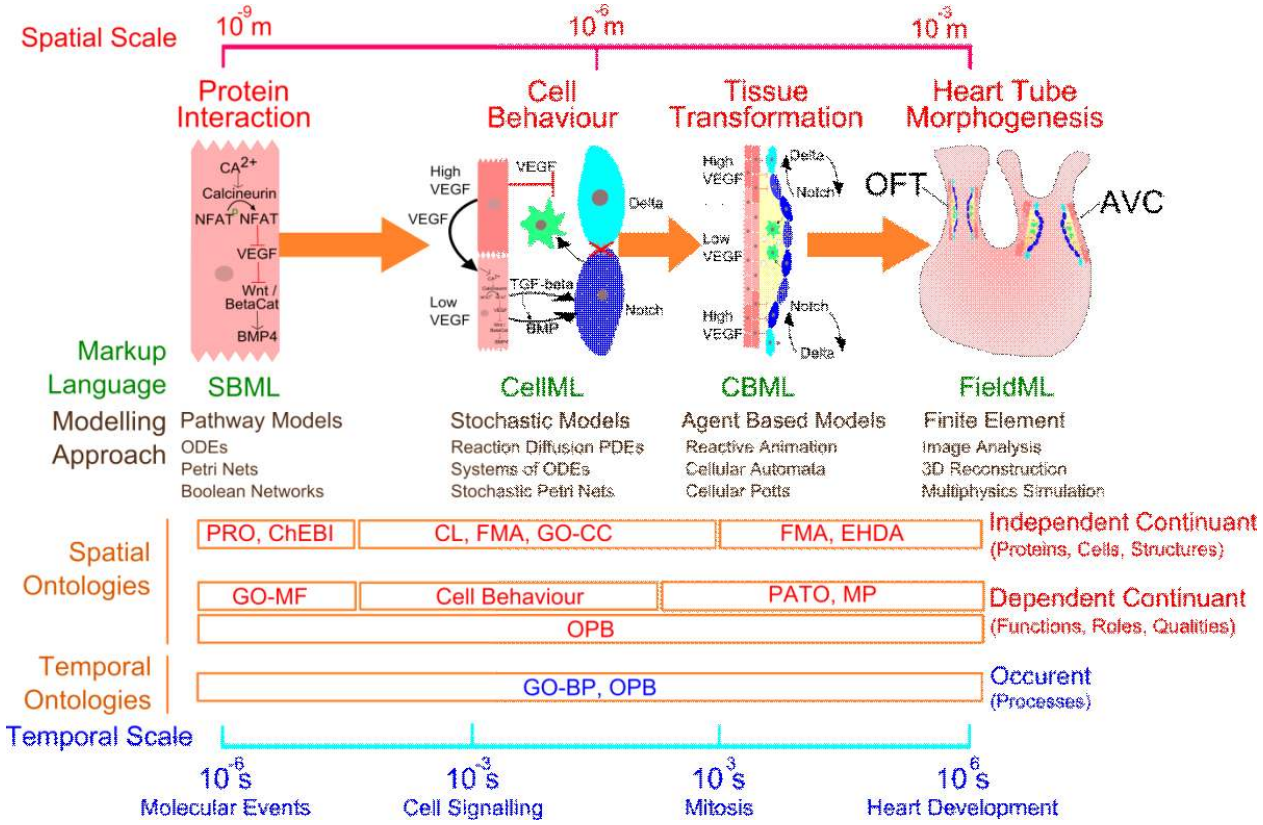

Fig. 3. Spatial and temporal scales of heart morphogenesis modelling initiative. The modelling framework encompasses spatial scales from 10-9m (proteins) to 10-3m (the primitive heart tube), and temporal scales from 10-6s (molecular events) to 106s (weeks of heart development). Modelling approaches appropriate to each level of scale are indicated, as well as markup languages that aid in the sharing of such models between platforms. Refer to Table 1 for acronyms.

phenotypic annotations from multiple ontologies. This defines the post-composition approach, which is described in detail in Section 4.

It has been argued that simple annotations (e.g. a pointer to a single reference ontology class) are insufficient for annotating the variety of data sources that need to be integrated within the current multiscale modelling projects [16]. The variety of possible classes increases due to the need for more highly specified annotations. To this extent the post-composition approach is necessary for fully integrated multiscale annotation. Furthermore, the Ontology of Physics for Biology (OPB) is intended as a means of encoding physical laws and systems dynamics that can be used in the post-composition annotation of model parameters and physical measurements. For example, to represent the link between fluid flow of blood in the aorta (in OPB – a dependent continuant ontology) with the structural property of a blood vessel (in FMA – an independent continuant ontology) the following statement can be used:

OPB:fluid flow is_property_of FMA:blood in the aorta

The same annotation is used, whether it is pointing to a model parameter or an actual biophysically determined flow rate. The OPB has been used as a means of integrating models, in different types of code, from different scales, by first converting them into lightweight semantic models [17]. This is currently a cumbersome process as an ontology is manually constructed for each model before mapping the terms. However the post-compositional approach with the OPBs ontological descriptions of physical laws and processes is part of what is needed for the integration of multiscale models.

Measurements provide parameters for models, as well as a means of comparing models to biological reality under different conditions. Models, on the other hand, are a means of formalising and refining hypotheses for documented biological phenomena and dependencies. Thus there is a clear need to incorporate both measurement and modelling under a common framework. Post-composition of well defined reference ontologies appears to provide the best means of doing this, with PATO providing the basis of phenotypic description, and OPB the basis of physical

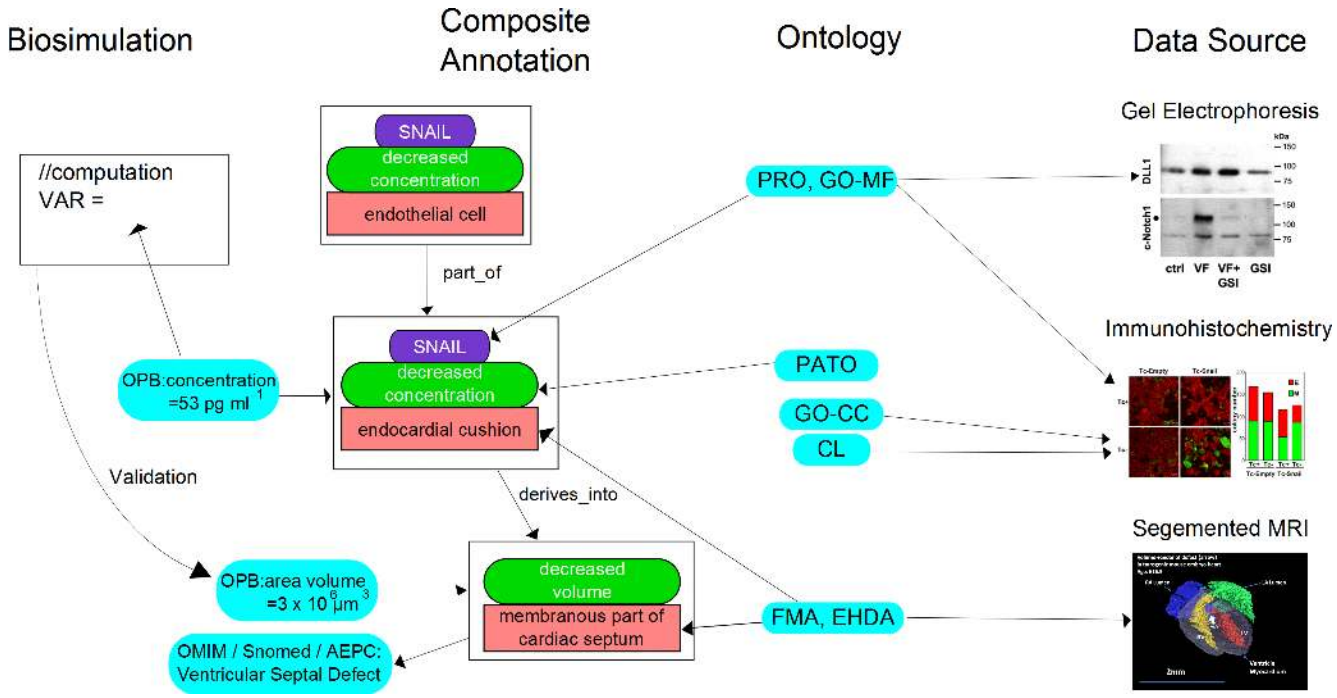

Fig. 4. Schema for composite annotation of biomedical data from multiscale sources. PATO allows for composite phenotype annotations allowing for representations such as 'endocardial cushion with decreased concentration of SNAIL', which are composed from multiple reference ontologies. OPB allows formalisation of the physical properties of these composite annotations, such as the concentration of a particular protein in a particular endothelial cell, or the density of mesenchymal cells in an endocardial cushion. These can then be used as variables in a computational model, or as validation of a simulation. PATO composites can be mapped to disease classifications, such as OMIM. Refer to Table 1 for acronyms.

properties and dependencies.

4 CASE STUDY

A major challenge is to provide information models for phenotypic data at each level of scale encountered. Model organism databases do this already using the Entity-Quality (EQ) formalism. In general, EQ associates an entity term from a species-specific anatomy ontology with a quality term from PATO [18]. There are reference anatomy ontologies for all the major model organisms, and for the case of the human this is called the Foundational Model of Anatomy (FMA), as indicated earlier. There are also developmental anatomy ontologies, and in this case the relevant ontology is the Human Developmental Anatomy (EHDA). It is straightforward to adapt the EQ formalism for developmental phenotypes. The initial step is to select the relevant ontology for the domain, as well as the types of sources that might be annotated. The process for the domain of heart development is shown in Fig. 4.

An EQ representation may be defined under a number of categories [19], with the example below taken from the process of heart morphogenesis.

Monadic states are those that involve single entities or structures. For example, it has been previously shown that some congenital heart abnormalities are caused by an incorrect rotation of the OFT. This can be annotated in a general way as:

EHDA:outflow_tract + PATO:mislocalised_radially

Relational states are those that describe a phenotype that exists between two entities or structures. For example, an endocardial cushion may be found to have a higher than normal concentration of VEGF-A. This could be annotated as:

FMA:endocardial_cushion + PATO:increased_concentration + PRO:VEGF-A

Composite states involve multiple phenotypes for a single state, which may be monadic or relational. For example, as shown earlier, DORV is a congenital heart defect where both the aorta and the pulmonary artery arise

from the right ventricle. In most cases this is also associated with a ventricular septal defect known as DORV Fallot Type. This defect could be annotated as:

FMA:aorta + PATO: associated_with + FMA:right_ventricle, FMA:pulmonary_artery + PATO: associated_with + FMA:right_ventricle, FMA:ventricular_septum + PATO:dysfunctional

This is a complex ontological description that comprises two relational states and one monadic state.

Quantitative states describe a measured value for a variable feature (e.g. size, area, count). For example, bicuspid aortic valve is a condition in which the aortic valve has two leaflets (instead of three). This would be annotated as:

FMA:cusp_of_aortic_valve + PATO:count="2"

To illustrate the remaining workflow involved in multiscale systems engineering, the team is in the process of developing simulations of endocardial cushion development via EMT [20]. These cushions are the structures that underlie the development of the heart valves and membranous septa, so are vital to understanding normal and abnormal development. Compucell3D [21] is being used as the modelling environment, which allows the specification of parameters such as cell target volumes, surface areas, adhesion, motility, proliferation and transitions between cell types. The secretion, diffusion and decay of chemical fields can also be specified.

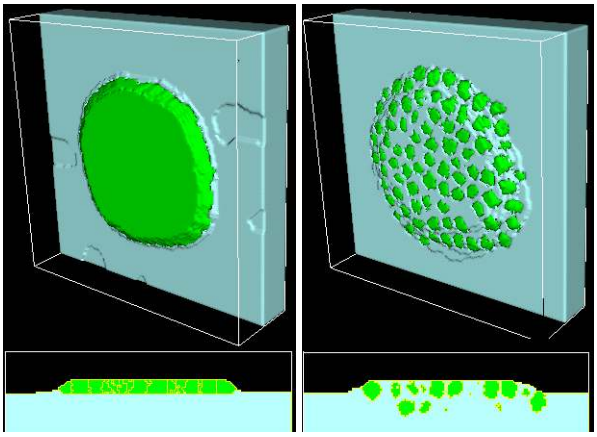

Fig. 5. Simulation of in-vitro EMT in Compucell3D. Cells initially forming an endocardial monolayer invade collagen gel upon loss of endocardial-endocardial adhesion and gain of endocardial-gel adhesion.

There are several theories on the signalling pathways that mediate endocardial cushion growth, each corroborated by *in vivo* [22] or *in vitro* [23] experimentation. The ability to simulate cellular movement and responses to different protein concentrations will enable us to understand the mechanisms of their interaction. From these interactions it may be possible to uncover any emergent effects of a single change in a concentration on cell behavior. In future, it should be possible to incorporate intracellular models of signal transduction pathways to more accurately determine concentration changes within individual cells. There is an emerging method that uses SBML reaction network models within the Compucell3D environment [24]. Peer-reviewed libraries of such models are available for re-use, for example the BioModels database [25], which accelerates the implementation of new combinations of model components.

Combining the knowledge gained from the information models (EQ formalism) allows the closure of the loop between physical experiments (real world) and computer-based simulations (model world). As the EQ annotations of the model world map to their isomorphic physical counterparts in the real world it is possible to be unambiguous about referring to (say) endocardial cells or increased concentration of a given protein.

5 DISCUSSION

With post-composition, there is a lack of exact consistency in annotations between different annotators [18]. This is not always a major problem because, with sufficient guidelines, the differences are usually ones of specificity (e.g. did they use the FMA term 'endothelium', 'endothelium of endocardium' or 'endothelium of aortic valve'?). These annotations are still valid semantically, but where a more coarse term is used there is a degree of information loss, to be avoided where possible. Restriction to terms of a specific domain and the use of customisable software tools for annotation improves consistency. An example of the latter is Phenote, an open source toolkit that facilitates annotation of biological data using OBO-format ontologies.

However, it is still possible to have different perspectives on the same physiological phenomenon. For example, one decision might be whether the interest is in the decreased volume of the membranous septum, or the fact that the membranous septum is dysfunctional. From the perspective of exact volume quantification the actual size measurement is important, whereas in the more general disease classification the interest lies only in the fact that there is a dysfunction.

There are often pre-composed terms in existing ontologies, which could also be made by post-composing terms from multiple ontologies. For example, in the MP ontology the term 'abnormal outflow tract development', could be composed as:

GO:outflow_tract_morphogenesis + PATO:abnormal.

The advantages of post-composition can be demonstrated here, because in the MP ontology, the only specific term relating to incorrect rotation of the aorta and pulmonary artery is 'transposition of the great arteries' (TGA). Whereas a TGA type defect is only one example that can arise due to incorrect rotation, two different types of transposition are possible: ˜45 degrees in the normal direction of rotation (dextro-TGA) or ˜45 degrees in the opposite direction (levo-TGA) (see Fig. 2). The degree of variability possible here demonstrates the advantage of post-composition: congenital heart diseases are a spectrum of overlapping phenotypes, and it is necessary to have flexibility in the way they are annotated. This accuracy in genotype-phenotype annotation, while arguably more complex, is more beneficial to wider biological research than mere coding of defects for the sake of classification. However, the strategies are not mutually exclusive: MP classes can be defined as cross products of terms from other ontologies, and this gives the best of both worlds. An intriguing possibility is to map anatomical measurements (such as those determined from the MRI of congenital heart disease specimens) to disease classifications. In the example shown in Fig. 4, ranges of degrees of outflow tract rotation could be used to classify different states (for example 140-160 degrees could be classified as 'normal outflow tract development' and anything outside this range could be classified as 'abnormal outflow tract development'). A similar approach could be taken with the position and sizes of the septa, valves and walls of the heart.

6 CONCLUSIONS

The challenge expressed in this paper was to correlate cellular and protein interaction models of processes such as EMT and neural crest cell migration with data that describe higher level morphology. Gene to phenotype (disease) associations are increasingly accessible [26]. These tend to use nomenclatures such as the European Paediatric Cardiac Code shortlist developed by the Association for European Paediatric Cardiology [27], which uses a surgical or anatomical perspective. While this is useful, the gene to phenotype annotations that need to be made of relevance to congenital heart disease, are not always of a 'one gene to one disease' nature. The reality is that several genes are implicated in several mechanisms, which may lead to one of several diseases [12]. The only practical way to enable such proliferous multiscale annotation is through a post-compositional approach, in which entities from several reference ontologies may be combined on the fly.

Model organism databases are well ahead of human biology databases in terms of having well defined semantics and interoperability, primarily through the GO, but increasingly through the post-compositon of PATO and other ontologies through Phenote. This is partly because it is possible to manipulate model organisms, and thus there is a vast abundance of specimen data. However, the increase in non-invasive, high-resolution measurement techniques, and the falling cost of genetic analysis, indicates that it is timely for human biology to catch up. Creating accurate phenotypic descriptions, which retain their semantic context, and linking these to physical and biophysical measurements, provides a powerful means to assimilate information from a wide variety of sources and scales. To this end the team has access to a unique physical resource – over 50 post mortem heart specimens that have been diagnosed as tetralogy of Fallot. The intention of future work is to provide MRI data of these specimens to link between the primary evidence and the degree of OFT rotation.

A further limitation to overcome is the lack of exact consistency in ontological annotations. Nevertheless, data sources of different types, at different scales have been identified, alongside the ontologies suitable for annotation, modelling methods at different levels, and initial guidelines for composite annotation. This demonstrates a method for creating a link between multiscale measurement and multiscale modelling that assists in closing the loop between physiological and genetic understanding of cardiac development.

APPENDIX A GLOSSARY OF TERMS

- AVC - Atrioventricular Canal
- BFO - Basic Formal Ontology
- CellML - Cell Markup Language
- CheBI - Chemical Entities of Biological Interest
- CL - Cell Type Ontology
- EHDA - Edinburgh Human Developmental Anatomy
- EQ - Entity-Quality
- FieldML - Field Markup Language
- FMA - Foundational Model of Anatomy
- GO-BP - Gene Ontology Biological Process
- GO-CC - Gene Ontology Cellular Component
- GO-MF - Gene Ontology Molecular Function
- MP - Mouse Phenoptype
- MRI - Magnetic Resonance Imaging

- OFT - Outflow Tract
- OPB - Ontology of Physics for Biology
- OMIM - Online Mendelian Inheritance in Man
- PATO - Phenotype and Trait Ontology
- PRO - Protein Ontology
- SBML - Systems Biology Markup Language
- VEGF-A - Vascular Endothelial Growth Factor – A

REFERENCES

[1] See www.physiome.org Last accessed on 23rd February, 2011.

[2] J.B. Bassingthwaite, "Strategies for the physiome project," *Ann. Biomed. Eng.*, vol. 28, pp. 1043-1058, 2000.

[3] See www.vph-noe.eu Last accessed on 23rd February, 2010.

[4] N.L. Novere, M. Courtot and C. Laibe, "Adding semantics in kinetics models of biochemical pathways," in *Proceedings of the 2nd International ESCEC Symposium on Experimental Standard Conditions on Enzyme Characterizations*, (Rhein: Beilstein-Institut), pp. 137-154, 2007.

[5] D. A. Beard et al., "CellML metadata standards, associated tools and repositories," *Phil. Trans. R. Soc. A*, vol. 367, pp. 1845-1867, 2009.

[6] B. Smith et al., "The OBO foundry: co-ordinated evolution of ontologies to support biomedical data integration," *Nature Biotechnology*, vol. 25, pp. 1251-1255, 2007.

[7] D. Noble, "Modeling the heart - from genes to cells to the whole organ," *Science*, vol. 295, pp. 1678-1682, 2002.

[8] M.H. Tawhai, E.A. Hoffman and C.L. Lin, "The lung physiome: merging imaging-based measures with predictive computational models," *WIRES Syst. Biol. Med.*, vol. 1, pp. 61-72, 2009.

[9] M.L. Kirby, *Cardiac development*. Oxford: OUP, 2007.

[10] V.M. Christoffels, G.J. Smits, A. Kispert and A.F.M. Moorman, "Development of the pacemaker tissues of the heart," *Circ. Res*. vol. 106, pp. 240-254, 2010.

[11] T.M. Yelbuz et al., "Shortened outflow tract leads to altered cardiac looping after neural crest ablation," *Circulation*, vol. 106, pp. 504-510, 2002.

[12] F. Bajolle, S. Zaffran, and D. Bonnet, "Genetics and embryological mechanisms of congenital heart diseases," *Archives of Cardiovascular Diseases*, vol. 102, pp. 59-63, 2009.

[13] L.F. Donnelly and C.B. Higgins, "MR imaging of conotruncal abnormalities," *AJR*, vol. 166, pp. 925-928, 1996.

[14] A. Restivo, G. Piacentini, S. Placidi, C. Saffirio, and B. Marino, "Cardiac outflow tract: a review of some embryogenetic aspects of the conotruncal region of the heart: the anatomical record - part A," *Discoveries in Molecular, Cellular and Evolutionary Biology*, vol. 288, pp. 936-943, 2006.

[15] C.L. Smith, C.A.W. Goldsmith and J.T. Eppig, "The mammalian phenotype ontology as a tool for annotating, analyzing and comparing phenotypic information," *Genome Biology*, vol. 6, R7, 2005.

[16] D.L. Cook, J.L.V. Mejino, M.L. Neal and J.H. Gennari, "Composite annotations: requirements for mapping multiscale data and models to biomedical ontologies," in *Proceedings of 31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, (Minnesota: USA) pp. 2791-2794, 2009.

[17] M.L. Neal, J.H. Gennari, T. Arts and D.L. Cook, "Advances in semantic representation for multiscale biosimulation," in *Proceedings of Pacific Symposium on Biocomputing 14*, (Hawaii: USA), pp. 304-315, 2009.

[18] C.J. Mungall, G.V. Gkoutos, C.L. Smith, M.A. Haendel, S.E. Lewis and M. Ashburner, "Integrating phenotype ontologies across multiple species," *Genome Biology*, vol. 11, R2, 2010.

[19] J.P. Balhoff et al., "Phenex: ontological annotation of phenotypic diversity," *PLoS ONE*, vol 5, e10500, 2010.

[20] T. Abdulla, R.A. Imms, J.M. Schleich, and R. Summers, "Systems modeling of EMT cell signaling pathways in heart valve development," in *Proceedings of VPH 2010*, (Brussels: Belgium), 2010.

[21] M.H. Swat, S.D. Hester, R.W. Heiland, B.L. Zaitlen, and J.A. Glazier, "Multi-cell simulations of development and disease using the CompuCell3D simulation environment," *Methods Mol. Biol*. vol. 500, pp. 361-428, 2009.

[22] J. Yi et al., "Endothelial SUR-8 acts in an ERK-independent pathway during atrioventricular cushion development," *Developmental Dynamics*, vol. 239, pp. 2005-2013, 2010.

[23] E. Delot, "Control of endocardial cushion and cardiac valve maturation by BMP signaling pathways," *Molecular Genetics and Metabolism*, vol. 80, pp. 27-35, 2003.

[24] See http://ryanroper.wordpress.com/2009/07/17/compucell3d-and-soslib-a-match-made-in-heaven/ Last accessed on 23rd February 2011.

[25] C. Li et al., "BioModels database: an enhanced, curated and annotated resource for published quantitative kinetic models," *BMC Systems Biology*, vol. 4, p. 92, 2010.

[26] R. Barriot et al., "Collaboratively charting the gene-to-phenotype network of human congenital heart defects," *Genome Medicine*, vol. 2, p. 16, 2010.

[27] J.P. Jacobs et al., "Congenital heart surgery databases around the world: do we need a global database?," *Semin. Thorac. Cardiovasc. Surg. Pediatr. Card. Surg. Annu*., Vol. 13, pp. 3-19, 2010.

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