

PROGRESS ON MEASUREMENT IN MEDICINE AND BIOLOGY: A MULTISCALE SYSTEMS ENGINEERING APPROACH

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Abstract – The theme for this keynote presentation is one of change; it recognises the paradigm shift from treating ‘illness’ to promoting ‘wellness’ while at the same time reporting the need for a multidisciplinary multiscale systems approach to the representation of physiological attributes and behaviour. Embryonic development of the cardiac cushions that eventually become the heart valve flaps is used as a case study to illustrate the utility of the multiscale systems engineering approach.

Keywords physiome, information, model

1. INTRODUCTION

Measurement in medicine and biology can be typified by physiological measurement of chosen variables that describe or explain underlying normal or pathological phenomena. One is then able to treat an illness based on this evidence, taken together with other clinical signs and symptoms, family history and the like. Traditional measurements include a determination of signal trends (e.g. electrocardiogram, electroencephalogram), physical flows (e.g. blood flow in a coronary artery), rates (e.g. heart rate, respiratory rates), physical pressures (e.g. arterial blood pressure), inputs and outputs (e.g. fluid balance), and concentrations (e.g. metabolites). Then there are the derived measurements and scores – such as heart rate variability and Glasgow Coma Score that provide summary information by combining data in a standard way. These physical measurements are supplemented by data and information that stem from imaging technologies. Trends in the uptake of integrated measurement systems to solve real world clinical problems using different combinations of these data can be detected. Rising costs of healthcare is acting as a driver for both organisational change and an increased rate of the adoption of technological change. There is a clear attempt by clinical managers to reduce the ‘length of stay’ in expensive hospital settings by increasing the burden on care in the community where the patient remains at home for treatment and recovery. There remains a need for home-based healthcare to provide physiological measurement for data monitoring as well as provide a means to transmit these data to clinics for patient assessments. Technical solu-

tions involved in this change include telecare and telehealth technologies, able to collect and transmit data using robust, easy to use devices. Other technological advances along the same axis include ‘wearable’ data collection devices, where perhaps sensors are sewn into the material of vests or shirts/blouses. A correctly positioned accelerometer will provide information on whether a patient is upright or supine, and can therefore detect falls in the home. Use of an RFID placed in the inner sole of a shoe can provide location information for (say) patients with dementia. A smart phone with in-built GPS can provide a similar solution.

A second axis of change is associated with a change in mind set of what health systems are for and how they can be used. Again there are clear signals from the funding agencies who support research that advances are needed in disease prevention and health promotion. The agenda has changed from just treating ‘illness’ to include promoting ‘wellness’. Here, the same home-based monitoring devices that allow patients to leave hospital earlier than before can be used to monitor continued well-being.

Though the work summarised above is clearly important and provides both impact and value to clinical decision-making, the focus of this paper is on a paradigm shift in medicine and biology brought on by technological advances and the measurement science that underpin them. It is widely anticipated that the 21st Century will be the biologist’s century to excel, just as the physicists did in the last century. The biologist’s century started well, with the sequencing of the human genome in 2001 – a process which means that all genes and proteins that they encode for are known and have been catalogued. These data and information are generally available, though their content may be distributed in databases in various locations around the globe. Although researchers are beginning to identify genotype to phenotype interactions, one might argue fairly successfully that the full extent of using the human genome sequence remains yet to be fully explored and exploited. Hence the paradigm shift; as discussed above there is already a perceptible move from ‘treating illnesses’ to ‘prevention of disease’ and ‘wellness’. Here, it is anticipated

that molecular medicine will have a huge impact. Costs involved in sequencing the genome have spiralled ever downwards whereas at the same time the number of active sites on chromosomes that have been associated with a particular phenotype have increased. It is likely to become common practice for individuals to have a copy of their own genome sequence, able to be used for what is termed ‘personalised medicine’.

2. MULTISCALE SYSTEMS ENGINEERING

Multiscale systems engineering can be defined as a group of methods, tools and techniques used to solve physical problems that have important features in multiple spatial and/or time scales. To take advantage of personalised medicine requires a link between the genome and the diasporas of cells and tissue types that represent the end of the signalling chain. In fact, there are recognised levels of scale in both the spatial and time domain that represent the intermediary stages of phenotype development. For instance, in the spatial scale there is the protein level (10^{-9} m), the cell level (10^{-6} m), the tissue level (10^{-3} m), and the organ level (10^0 m). The tools and techniques used to understand the physiological phenomena vary according to the level of scale, but include mathematical modelling using ordinary and partial differential equations, stochastic models, and pathway (network) models. In the absence of a specific multiscale modelling programming language, scale linking (that is the method by which models of different scales are integrated), is achieved currently by linking the ontological information that underpins and relates the terms used to each other.

Though multiscale systems engineering is being applied to all human organs through a worldwide research initiative known as the Physiome project, which is being co-ordinated by Peter Hunter and his group at Auckland University [1], the dynamics of cardiac function are attracting a lot of attention. By far the majority of the work is investigating the normal and diseased adult heart. In contrast, the research group at Loughborough University, together with research partners in Rennes and Paris, is one of only a few centres that is looking at the heart as it develops in the womb [2]. Specifically, the international team is attempting to further understand the multiscale processes that give rise to a congenital heart defect known as the tetralogy of Fallot (ToF). One of the four signs that define this condition is a septal defect in the wall that separates the right and left ventricle. The septum itself is formed as a result of epithelial to mesenchymal transition (EMT), and it is this process that we first wish to understand from a multiscale perspective.

3. CASE STUDY

3.1 Anatomic Level

Cardiac development commences in week 2 (embryonic day 14 - E14) of gestation and is fully formed

by week 8. It is in week 2 that the first cardiac milestone is achieved. Though the primitive heart is in the shape of a tube at this stage, the cardiac muscle is developed sufficiently for muscle contractions to occur, and as a consequence blood flow through the cardiac tube. This activity can be measured via electrophysiological recording of the primitive heart beat [3]. The walls of the heart tube comprise three layers: endocardium; ‘cardiac jelly’; and an outer layer of myocardium. At specific sites in the heart tube on around E26, the cells of the endocardium start to take on a mesenchymal phenotype and at the same time invade the middle cardiac jelly layer of the heart tube wall. This causes localised swellings termed ‘endocardial cushions’ which are the precursors of heart valves and the inner wall structures of the heart. E26 is also a milestone in anatomic structure of the developing heart as two simultaneous processes termed ‘looping’ and ‘wedging’ take place, allowing the final structure of the heart to be realised by about E32.

E26 to E32 is a crucial time in the development of the embryonic heart, as congenital birth defects due to abnormal looping and wedging become apparent at this time.

3.2 Cellular Level

The endocardial cushions mentioned above play a crucial role in the formation of the inner structures of the heart – the heart valves, the septa and the trabecular musculature of the left ventricle. EMT is the underpinning cellular process, so it follows that abnormal EMT leads to (typically) a septal defect (more commonly known as a ‘hole in the heart’). EMT occurs because endothelial cells lose their adhesion to each other. This process has been simulated using a Cellular-Potts model that demonstrates different scenarios depending on level of adhesion. Results show a good similarity in behaviours between the *in silico* and *in vitro* models.

3.3 Protein Level

Several signalling pathways have been identified as important in EMT. To continue the argument being developed for endothelial cell adhesion to be a central player in normal heart development, the *notch* family of proteins also play an important role. In the endocardium *notch 1* is expressed in cushion forming regions, but not expressed in other regions; whereas it is the other way around in the myocardium. *Notch* also activates genetic transcription of the *snail* family of proteins, which in turn inhibit transcription of the protein *VE-Cadherin*. It is this latter protein that aids cell adhesion. Thus an activated *notch* protein signalling network induces a loss of cohesion. Mutations in genes that encode the *notch* signalling proteins can therefore lead to congenital heart disease. In particular, mutations in *JAG1* (a ligand for notch receptor proteins) are associated with tetralogy of Fallot.

3.4 Genome level

A hypothesis put forward by Bajolle [4] suggests that a heart defect may originate from different embryological mechanisms including a formation abnormality of the endocardial cushions. The complexity of the multiscale representation increases, as these mechanisms are controlled by multiple genes (e.g. *Pax3*, *Pitx2*, *Tbx1*, *Fgf8*, *Bmp*). The result is a concept known as ‘one heart disease – several mechanisms – several genes’. As there is redundancy in the gene regulatory networks that control heart development, mutations in several different genes acting through many mechanisms can lead to the same disease phenotype. Equally, a disease phenotype might be caused by one of several different mutations, as more than one gene controls each developmental mechanism.

4. DISCUSSION

The paper has considered advances in measurement in medicine and biology. While important strands of work have been alluded to that refer to the use of telemedicine and wearable systems to drive down the anticipated costs of healthcare, the case study introduced a new method that investigates a system from a holistic stance. Multiscale systems engineering is not restricted to biomedical applications, as the approach is starting to be used in chemical engineering and materials science. In both of these cases, the work tends to be industry led, as they see a way to make improvements in processes that may develop into unique selling points for competitive advantage. The case study has shown the utility of the multiscale systems engineering approach with an application in human embryology and physiology. However, no matter what the application domain, issues remain. These issues include the development of novel data collection methods that are applicable across all spatial scales simultaneously; the same issues arise for representing the data and information in a way that allows for efficient and effective integration. In recent years there has been a lot of work on visualisation of data, the multiscale approach is a good test of these methods, where simultaneously occurring events might be evident across spatial scales, but might have different dynamics across the time scales. In *in silico* simulations multiscale model validation requires new methods that are as yet not in the public domain. In fact whereas there is a catalogue of methods, tools and techniques to attack problems at one level of scale, there are very few in the public domain that are truly applicable to multiscale problems. This leads to a further issue termed ‘scale linking’, or the ability to connect models together to demonstrate behaviour at more than one scale simultaneously. One method available currently is to convert the models used at adjacent spatial scales into a meta-computer language that essentially acts in a way to integrate structure and function. However, the Project Fallot team have used an alternative approach, that of ontol-

ogy-driven development to achieve the same end. Here, the team has taken advantage of the fact that clinical terms that are used in descriptions of entities at different scales occur in more than one ontology that overlap each other. This may be seen as a ‘work around’ rather than a fundamental solution but there is an option for further work in developing an integrated information system based on in turn information architectures, information models, and information configurations.

5. CONCLUSION

A multiscale systems engineering approach has been adopted to investigate a complex adaptive system characterised by identified and known failure modes in terms of congenital heart disease. It is clear that much work remains, not just on the application, but also on the methods and tools available to tackle multiscale investigations. One promising way forward might be to transfer knowledge gained in and between domains with each other. For instance, there is an opportunity for the Project Fallot team to apply their approach to problems in materials science and aeronautical engineering. It remains to be seen if the approach has the capability to solve problems from other domains.

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