**Multi-scale biomedical systems: measurement challenges**

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**Abstract.** Multi-scale biomedical systems are those that represent interactions in materials, sensors, and systems from a holistic perspective. It is possible to view such multi-scale activity using measurement of spatial scale or time scale, though in this paper only the former is considered. The biomedical application paradigm comprises interactions that range from quantum biological phenomena at scales of 10^-12 for one individual to epidemiological studies of disease spread in populations that in a pandemic lead to measurement at a scale of 10^+7. It is clear that there are measurement challenges at either end of this spatial scale, but those challenges that relate to the use of new technologies that deal with big data and health service delivery at the point of care are also considered. The measurement challenges lead to the use, in many cases, of model-based measurement and the adoption of virtual engineering. It is these measurement challenges that will be uncovered in this paper.

**Introduction**  
The aim of this paper is to uncover the measurement challenges that arise from a systemic appreciation of a disease process that affects both an individual and the population within which that individual belongs. By drawing a systems boundary that encompasses both individuals and populations is possible via a multi-scale approach to physiology and epidemiology. This approach can be defined as the consideration of physiological systems that possess measurable characteristics that can be exhibited at multiple spatial or time scales simultaneously. For this paper only multiple spatial scales are considered; and to demonstrate the variety of measurement issues and their ensuing complexity a snap-shot is taken at either end of the spatial scale under consideration (quantum level phenomena within an individual to epidemiological studies of populations) as well as an application-based intervention at the limit of the whole body level (telemedicine). Quantum biology can be defined as the purposeful use of quantum mechanics applied to the system of interest in order that some sort of biological advantage can be gained. Telemedicine at its most simple is the delivery of care at a distance using a digital network to connect and integrate component parts. Finally, epidemiology refers to measurement of some defined individual outcome within a specified population. Measurement challenges are likely to be different across the spatial scale, it is the purpose of this paper to uncover the nature of these differences as well as any similarities.

**Multi-scale biomedical systems**  
The traditional view of biology, physiology and epidemiology is to gain an understanding of a specified process via a reductionist approach. This systematic mode of thought and analysis is common place in engineering and science. However, there is evidence accumulating that a more systemic appreciation may bring dividends when trying to understand problems that surpass one level
of scale simultaneously. Perhaps the current best example of achievement in this field is the physiome project which collects and curates multi-scale physiological models from research groups throughout the world. An early description of this project demonstrates the model-based philosophy that still prevails [1]. The vast majority of the current work provides details of models that apply to structure and function of specified systems in the adult. To extend the application base as well as to explore measurement at the boundaries of current knowledge and understanding, a multi-disciplinary international team was brought together to investigate the utility of multi-scale models for cardiac morphogenesis, and more specifically epithelial to mesenchymal transition (EMT) of cells that form the internal structure of the heart [2, 3]. EMT will continue as a system of interest, as it has been shown that it also plays a role in wound healing and tumour growth.

**Quantum biology**

It is often quoted that should the 20th Century be labelled the ‘physicists’ century, then the 21st Century has potential to be the ‘biologists’ century. Perhaps no one topic fits that bill other than quantum biology – a discipline that is looking for a purpose. There are many missing pieces of the jigsaw that would allow a complete picture to be elucidated, held back by the lack of a formalism to describe the state space of biological systems and their dynamics in quantum theoretical terms. Thus the discipline is immature mainly due to the difficulty of controlling, measuring and modelling quantum level systems. However, measurement challenges can still be discerned and relate to: adequacy of language used to describe interventions, the exact system information needed, the lack of experimental design, as well as the completeness (or lack of it) of the theory that underpins the measurement. There still remains a gap between the disciplines of quantum physics and the physical principles of quantum biology but exploring this gap has potential to reap rewards in terms of yielding new and interesting results. In roads have already been defined through the study of quantum biology in photosynthesis [4], magneto-reception [5], olfaction [6], vision [7], and early reviews of the discipline [e.g. 8].

**Telemedicine**

The increasing burden of disease caused by the ageing population coupled with ever-increasing costs of hospital-based healthcare have created a perfect storm out of which has emerged the need for telemedicine-based interventions that enable swifter hospital discharge and delivery of care in the community. To a large extent telemedicine relies on patient engagement with self-management and though the measurement challenges are not limited to patient-technology interactions, there are still some that can be alleviated by better education and training opportunities. Some of the issues relate to: time of measurement, missed measurement, proxy measurement, incorrectly inputed data. As an example in the last category, consider the routine measurement of blood pressure, say by an automatic sphygmomanometer. The cuff may be incorrectly placed anatomically; the cuff may be placed on top of a shirt/blouse; the sphygmomanometer itself may need calibrating, or the traceability chain may be broken. The full paper will draw upon experiences from EU Doc@ Home

**Epidemiological studies**

The major measures of disease in a population are related to prevalence and incidence, where the former measures existing cases of disease (or other outcome) and the latter measures new cases of disease within a specified population. In fact there are two measures of both in common practice. Point prevalence is the proportion of individuals in a defined population that possess the health outcome of interest at a specified point in time; whereas period prevalence is similar though measured over a specified time period. As an example of point prevalence consider a UK General Practitioners Surgery list of 20,000 outpatients on 1st August 2016, should 400 of them have diabetes the point prevalence of diabetes within the given population is 400/20,000 which is 0.02 or 2%. So although prevalence in this simple example provides an example of disease burden at the given GP surgery, it assumes that diagnostic accuracy is 100% with no Type I or Type II errors. The two main measures of incidence are termed incidence risk and incidence rate. Incidence risk is the more straightforward of the two to adopt
and is the proportion of individuals in a population that were initially free from disease but who have been contaminated within a specified time period. This measure assumes that there are no naturally immune individuals in the given population and, of course, individuals may die within the study period, move away or indeed move in to the area of interest. It is incidence rate that is perhaps the more purposeful of the two measures and tries to take into account some of the measurement issues associated with incidence risk by using the sum of the time that each individual has remained at risk of developing the disease (or other outcome) of interest. To adopt incidence rate there is thus the need to calculate a factor ‘person-time at risk’ which itself has several sources of measurement error. This factor is defined as the sum of each individual’s time at risk over a given time period (usually months or years). Should the individual develop the disease/outcome, die, migrate, (s)he is no longer at risk and therefore cease to contribute to the factor. Clearly tracking of each individual in the population is extremely important to obtain a true measure of incidence rate. Poor study management can cause an underestimate of the true incidence rate. Prevalence and incidence are related by the following equation:

\[ P = ID \]

Where P is Prevalence; I is Incidence rate; and D is the average duration of the disease.

In most epidemiological studies it is rare to use the complete population of a geographical area as the given population, instead a population sample is used. The population sample should be a representative of the whole, but inter-comparisons between outcomes measured from different samples from the same population have shown that this is not the case. Differences occur due chance variations in each of the samples, but the crux of the issue is that it is not known whether the variation causes an overestimation or an underestimation of the true value. Statistical tests are available that measure this chance effect and are related to ‘standard error’ measures. When comparing results within a population sample, the standard error can cause Type I or Type II errors: rejecting the null hypothesis when it is true (true negatives) and accepting the null hypothesis when it is false (false positive). Study design is aimed at reducing the sampling error which can be accomplished by allowing the population sample to be as large as possible. There are also measurement errors associated with the research methods used within the study design: lack of or incomplete data, bias, confounding variables, temporal sequence between having a disease or not may be fuzzified (e.g. by having a susceptible population), and so on.

**Conclusions**

This paper has considered measurement issues and challenges across the spatial scale spectrum and it is clear from the snap-shot approach used that most challenges are unique to a particular level of analysis. However there are also similarities – for each there is a gap between conceptualisation and realisation. Another reason for choosing the three areas is the difference in maturity of the measurement methods associated with systemic intervention. Epidemiology has been with us the longest so it is not unusual to see the bank of well-validated statistical methods associated with reducing the standard error. If leading edge telemedicine applications are ignored, it has been available since the 1990s. It can be argued that further methods need to be adopted before acceptance by the general public. Should we ignore Schrödinger [9] and the like who worked individually at different points in the twentieth century, then quantum biology is the newest sub-discipline. There remains much to do to gain acceptance within the scientific community before exposure to the general population. It is quantum biology where the leading edge now lies, perhaps waiting for novel visualisation methods to allow accelerated development of its purposeful use in biology and medicine.
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