Proceedings of 2017 IEEE
International Conference on Mechatronics and Automation
August 6 - 9, Takamatsu, Japan

A Review of Multiscale Science: Materials, Biology, Multiscale Data Analysis and Examples from Complex Physiological Systems

Jiaqi Liang[1,2]

[1]Institute of Automation, Chinese Academy of Sciences, Beijing 100190, China

[2]University of Chinese Academy of Sciences, Beijing 100049, China

liangjiaqi2015@ia.ac.cn

***Abstract* - Multiscale science is an emerging scientific field that spans many disciplines, including physics, chemistry, materials science, mathematics, and chemical engineering, etc. Therefore, the multiscale methodology has received increasing attention from many branches and researchers. This review firstly introduces the general developmental situation including theoretical basis, scales, and relevance, as well as some progress in several fields. Based on the facts that it would be impossible to carry out a serious discussion deeply with such a broad view, we secondly adopt a narrower viewpoint. Unlike most of the papers focusing on the multiscale problems in chemistry or materials science, we will emphasize the issues in data analysis of complex physiological systems where the multiscale character is the dominating role and is exploited innovatively. Finally, this paper elucidates the future challenges of multiscale science.**

Index Terms* - *Multiscale science, Scales, Relevance, Complex systems and Physiological data analysis

I. MULTISCALE SCIENCE

A. *Multiscale Phenomena*

Many phenomena in nature involve multiple active scales. Whether we explicitly recognize them or not, they are part of our daily lives. From the viewpoint of physics, all materials at the microscale are made up of nuclei and electrons, whose structure and dynamics are responsible for the macroscale behavior of the material, such as wave propagation, deformation, and failure [1]. In biology, the interactions between molecules occur on a space scale of nanometers and a time scale of nanoseconds. However, the interactions on the cellular level require considerably larger space and time scales [2]. In the age of information exploration, a large volume of observational data involves profuse multiscale phenomena itself. A time series may show rising trend in large time scale, but contain fluctuations in small time scale.

Besides, many real systems are complex, consisting of relatively separate subsystems that each contribute to the overall system. These subsystems each take place on a specific scale, which makes the research cannot be limited to monoscale.

Some experts [3] pointed out that multiscale phenomena were the most challenging fields. The need for multiscale simulation and modeling is pervasive in many areas of science and engineering. Fundamentally, new multiscale mathematics, considerable framework of multiscale computation and even software are required to address the challenges of multiscale issues. Thus, multiscale science should be treated as a promising independent subject [3].

B. *Research on Multiscale Science*

Multiscale phenomena are inherent in the objective world, but the multiscale science was put forward in recent years and it has become a hot issue. Multiscale science is the study of phenomena which couple distinct length or time scales [3]. With the advancement of the study, there has been more diversified comprehension in scales, which will be discussed in the next section. In short, multiscale science cuts across almost all of science.

Multiscale science is growing so rapidly that it has emerged as a new independent multidisciplinary scientific field. A Society for Industry and Applied Mathematics (SIAM) Interdisciplinary Journal *Multiscale Modeling and Simulation* started in 2003 by T. Y. Hou. It aims to develop systematic modeling and simulation approaches for multiscale problems. Another International Journal of Multiscale Computational Engineering also started in 2003, pointing to the rapid evolution of multiscale science. Meanwhile, there have been many symposiums on multiscale problems. Three multiscale mathematics workshops were organized by U.S. Department of Energy (DOE) in 2004. The first workshop was about Multiscale Modeling and Simulation, including three methods (Multiresolution Discretization Methods, Hybrid Methods, and Closure Methods) and six target applications [4]. The second workshop was about the current state of mathematical methods for multiscale problems, including four Mathematical Techniques (Adaptive Discretization and Modeling, Variational Multiscale Analysis, Discrete to Continuum Bridging and Reduced Order Modeling) and three applications [5]. The third workshop was about the Multiscale Mathematics Needs, including eight methods and nine cases (climate, biosciences, and fusion, etc.) [6].

The research on multiscale science can be concluded into three main aspects: the description of multiscale phenomena, the mechanism analysis and the association of multiscale phenomena. To describe the multiscale phenomenon is to decompose the complex process and select the appropriate scales to analyze. The mechanism analysis is to reveal the physical mechanism of multiscale phenomena from the micro dynamics to macroscopic phenomena. Such a process can

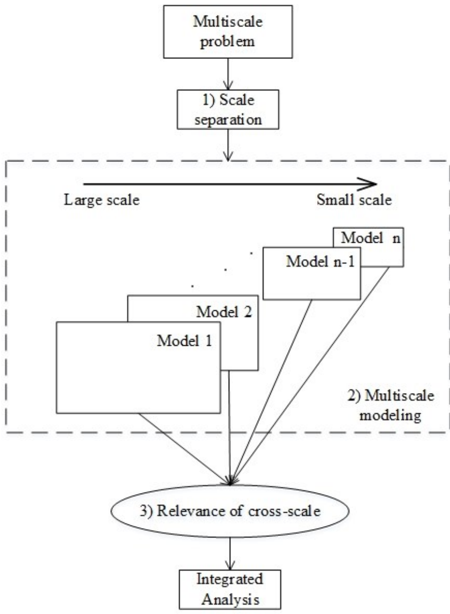

Fig. 1 General ideas for solving multiscale problems.

reflect the evolution of systems and will be an important breakthrough in the future study. The association of multiscale phenomena mainly refers to the relevance across different scales and scale conversion. These three aspects are not independent of each other but often interact and permeate mutually [7].

Although there are different methods according to the different situations, the general ideas for solving multiscale problems are as follow:

1) Scale separation: Multiscale structure involves a variety of complex processes which take place on their own scales. The complex system can be transformed into several relatively simple subsystems in different scales so that the whole problem can be simplified and partially decoupled. How to devise and describe scales is central to multiscale methods.

2) Multiscale modeling: The direct analysis of the total problem can be difficult and may lose internal mechanism. So, modeling respectively and simultaneously for each scale divided in 1) provides a convenient way to recognize different levels of the system. And modeling for each single scale is simpler than the whole complex system. This is where multiscale modeling comes in.

3) Relevance of cross-scales: Modeling respectively in each scale provides a new perspective to solve multiscale problems, but all the scales interplay and consist a whole. Due to the coupling among scales, it is necessary to exploit the relevance of adjacent scales. The models for each scale and the relevance of cross-scales constitute the integration model which describes the complex multiscale issues.

There have been several classical success examples of combining models at different scales to model multiscale processes. For example, QM-MM [8] (quantum mechanics–molecular mechanics) approach is a procedure for modeling chemical reactions involving large molecules, by combining quantum mechanics models in the reaction region and classical models elsewhere. Indeed, compared with the traditional approach of focusing on one scale, looking at a problem simultaneously from several different scales and different levels of detail is a much more mature way to do modeling [1].

II. Scales and Relevance

A. *Scales*

Multiscale phenomena exist in every field, and the meanings of scales are not same in all disciplines. Small scale often refers to the relatively microscopic research object and large scale is on the contrary. Some researchers defined scales by space or time. However, the scales are no longer only divided by space or time, along with different research field. We summarize several perspectives mainly used to describe scale representation at present as follows:

1) According to time metric: E.g. Climate, chemical reactions, and stock forecasting, etc.

2) According to frequency: E.g. Digital Signal Processing, especially wavelet multi-resolution decomposition.

3) According to space metric (length or area): E.g. Materials, the biological system, and Geographic map building, etc.

What should be noticed is that time and frequency have the same essence in some cases of signal processing and data analysis. In addition to the three points mentioned above, the gas-liquid-solid in the heterogeneous reaction can also be seen as scales. In the field of image, scales are always connected with Gaussian kernel and down sample [9].

It is also noteworthy that even if the scale division is based on the same metric, the size of scales is diverse. For example, in the synoptic system, the basic feature of mesoscale atmospheric motion is the horizontal scale [10] from $2\times10^3\mathrm{m}$ to $2\times10^6\mathrm{m}$. That size of mesoscale is far more than the macroscopic scale ($\sim10^{-2}\mathrm{m}$) in Complex Dynamic Problems [11]. These fully illustrate the variability and subjectivity of the multiscale phenomenon.

B. *Relevance of Cross-scales*

In the traditional process of studying a system, we often explore the dynamic characteristics and then use control theory to achieve the purpose of controlling the system. The dynamic characteristics and the control strategies determine the control performance together. This causal relationship always guides our research and plays a vital role in the control and management of systems.

However, real systems always encompass interacting behaviors occurring across a range of scales. For complex systems, the relationship between the various scales is not often the causal relationship we desired because of its complexity. An essential issue in resolving the coupling between scales is how to connect large scales to small scales or create a continuum model. In many cases, the models and methods available at different scales need to be enhanced in order to provide the information required for adaptive decisions across scales [4].

On this basis, we propose a concept of ‘relevance’. Relevance is the relationship among different scales. The relevance is a representation of the interaction between the composition of different scales and the nonlinear cross-scale interaction in a system. Relevance is diverse. It may appear to have strictly deterministic functions, the dependent relationship which is hard to denote in the form of mathematic method, or even mutual restriction. In this way, the causal relationship can also be seen as a kind of relevance.

Although there is no mature definition and universal mathematical model for the relevance in multiscale issues, exploring the relevance helps to understand the evolution mechanism of complex systems. It may not be possible to obtain the optimal control strategy through the calculation and analysis as the traditional cybernetics, but it can provide decision support according to its description and facilitate the control and management.

Cross-scale relevance is very complicated and is a young field of research. Since some mature research methods at different scales have already been developed for some complex systems, cross-scale research methods have not yet achieved. There are still many problems that should be solved urgently. The development of cross-scale relevance of the theoretical concepts and research methods are also important in the future research. This section only points out some problems and gives our view on the relevance of scales, and also attempts to appeal to searchers for their attention to the research on related work.

III. MULTISCALE APPLICATIONS

As what was already discussed, multiscale science can be used in so many fields. So in this section, we first focus on several domains that are significantly improved by multiscale methodology. Outside of these domains, we also found a valuable multiscale project which was related to the multiscale physiological signal. We emphasize multiscale data analysis of complex physiological systems late in this section as a reflection of multiscale phenomena.

A. *Multi-field Applications of Multiscale Science*

1) Materials science: Multiscale problems permeate all of the materials science in both length and time scales. Better understandings of fundamental processes such as fracture and failure, nucleation, and electronic and transport phenomena that occur on multiple scales will require new mathematical tools and techniques [4].

Materials science applications are inherently multiscale, as the macroscopic properties of many materials are largely characterized by interactions occurring on the microscopic level [2]. The diverse outputs of multiscale methods are reflected in various aspects of materials modeling. A popular technique in this field is coarse-graining, in which multiple atoms are resolved as a single coarse-grained particle with a pre-imposed potential [12].

In 2002, as part of a survey of modeling techniques of structural materials, Porter [13] discussed a wide range of length scales which should be considered in materials problems, and some methods commonly used. Afterwards two further published reviews described some specific topic explicitly using a multiscale approach [14][15]. There have also been several symposia devoted to the topic ‘Multiscale modeling and phenomena of materials’ [16].

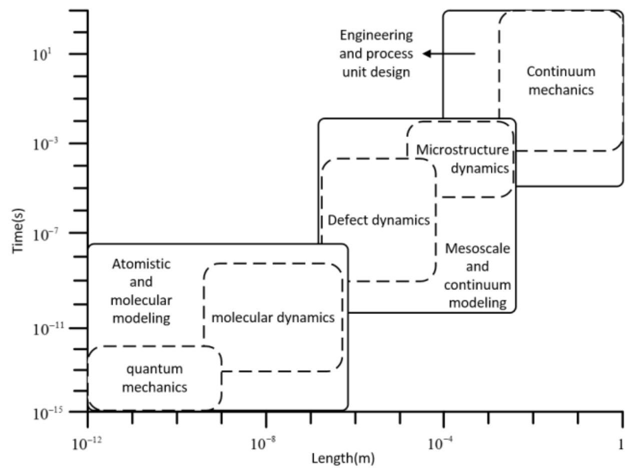

Fig. 2 Scales in materials and multiscale modeling techniques [17].

Fig. 2 shows approximate range of time and length scales covered by different methods. Areas of overlap permit ‘mapping’ or ‘zooming’ from one scale to the next, which often required for parameterization of higher scale methods or for obtaining a finer scale resolution of selected parts of the larger system [18].

2) Biology: Biological functions happen at several scales, so biological systems include many orders of magnitude through time and spatial scales. Obviously, the study of biological systems is greatly aided by multiscale methods that enable the coupling and simulation of models spanning several spatial and temporal scales [19]. For example, the human body spans many scales, ranging from the molecular scale up to whole-body processes [2].

Biology at each scale integrates information from scales above and below [20]. There are various types of scale in the biological systems. Southern and colleagues [21] used the organization of biological systems to classify the biological processes with a hierarchy of spatial scales, ranging from gene, proteins, individual biological cells, tissues, organs, and up to the individual organism. Associated with the spatial scales are the temporal scales of biological processes, ranging from microsecond (10^{-6}s) for molecular interactions to 80 years (10^{9}s) for the average human life expectancy [22]. The deep study of biological systems requires multiscale modeling which integrates the relevance that occurs on these diverse scales [19].

Currently, multiscale modeling in biology has already been widely used and reviewed. Dada and colleagues [19] provided an overview of multiscale modeling and simulation in systems biology and described the development of several multiscale methods covering various biological processes. In addition, several coupling tools were originally developed to construct biomedical multiscale simulations and many markup languages have emerged to exchange single-scale model definitions and system information, which is an important aspect of constructing multiscale models [2].

3) Multiscale data analysis: With the rapid development of information technology, data has penetrated into every domain. A great deal of information is included in the data generated during the running process of systems. Massive data with long duration, dynamic changes, and multiscale characteristic are changing the paradigm of scientific research. How to extract useful information from data and how to analyze the internal dynamic mechanism are still needed to be solved. However, some multiscale methods have been promoted to observe data trend in various scales and analyze data association.

Multiscale data analysis refers to the process which consists of the formation of multiscale data sets, multiscale data processing and analysis of data in different scales to reveal implied knowledge.

Using multiscale methods to explore data characteristics has been widely used in many kinds of fields. For example, Verhein and colleagues [23] provided a comprehensive definition of Spatio-Temporal Association Rules that described how objects move between regions over time and presented other patterns that were useful for mobility data. Jiang and colleagues [24] developed multiscale multifractal time irreversibility analysis (MMRA) which allowed to extend the description of time irreversibility and employed it to the analysis of stock markets in different regions. Zhang and colleagues [25] utilized the asymmetric multiscale detrended fluctuation analysis (A-MSDFA) method to explore the existence of asymmetric correlation properties for PM2.5 daily average concentration and to assess the properties of these asymmetric correlations. Huang and colleagues [26] developed a method called empirical mode decomposition (EMD) for analyzing nonlinear and non-stationary data with which any complicated data set can be decomposed into a finite and often small number of intrinsic mode functions.

B. *Multiscale Analysis of Complex Physiological Systems*

Complex systems are characterized by hierarchical multiscale nature with respect not only to space but also to time [27]. Multiscale is considered to be the emphasis in studying complex systems, particularly the relevance between different scales.

The complex physiological system contains physiological data which is rich in multiscale information. And there are abundant data sources for complex physiological system research. Physiological signals are generated by the interaction of multiple subsystems of living organisms, whose time and intensity are different ceased by time and space complexity of physiological activity. The physiological signal is the reaction of life state, the study of various physiological parameters has important applications and value. Successful physiological analysis requires an understanding of the functional interactions between the key components of cells, organs, and systems, as well as how these interactions change in disease states [28]. The traditional complexity analysis methods only consider the complexity of physiological signal on the single scale, which is not conducive to a comprehensive understanding of the dynamics of the system. Meanwhile, ignoring the information and relevance in different scales is not favorable for disease diagnosis. In this section, we focus on the multiscale analysis of physiological signals, especially Electrocardiogram (ECG) and RR (inter-beat) intervals.

The most widely used method is multi-scale entropy (Multiscale Entropy, MSE) proposed by Costa [29]. Currently, multiscale analysis has been used for ECG, EEG, HRV (heart rate variability), and other physiological signals, as well as the identification and detection of disease.

1) ECG signal scale separation based on EMD: The EMD method can decompose any complicated data set into a finite and often small number of intrinsic mode functions that admit well-behaved Hilbert transforms [26]. Since EMD method is based on the local characteristic time scale of the data, it is applicable to nonlinear and non-stationary processes [30]. Each intrinsic mode function (IMF) has the same length as the original data, which can avoid non-solution phenomena caused by the reduction of data length. After EMD decomposition, we can evaluate the energy and entropy distribution of physiological signals on each scale, and explore characteristic differences under different scales.

ECG is the signal that records the electrical changes within the heart at regular intervals. The horizontal plane of the ECG is time and the vertical plane is the amplitude of the electrical potential [31]. Electrical impulses occur as a result of polarization and depolarization. These impulses are presented as P, QRS and T waves, which involve different kinds of frequency. In this work, 11 IMFs are obtained from 20s ECG segment (data source: The PAF Prediction Challenge Database [32]) as shown in Fig. 3.

IMF1 and IMF2 contain higher frequency, mainly QRS waves. From IMF1 to IMF11, the frequency changes from high to low, with the small time scale to the large time scale. The large time scales reflect heart long term rhythm.

2) Multiscale analysis and visualization: Based on EMD, we extract various characteristic variables from each scale to

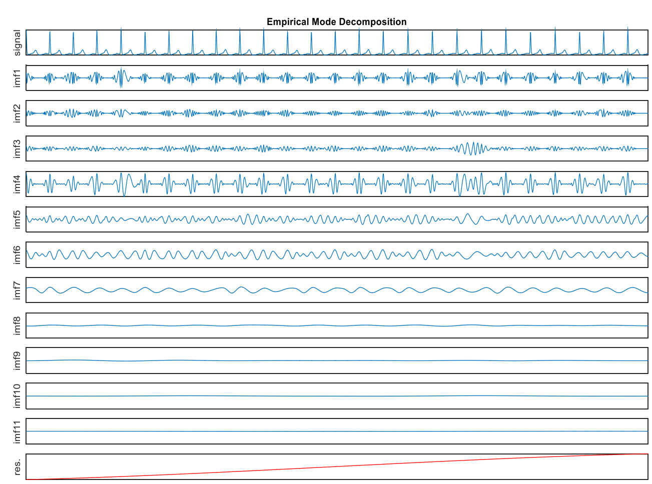

Fig. 3 IMFs of ECG signals.

discuss the physical meaning and the identification of the disease. Here, we choose RR intervals to show the difference between normal subjects and AF (Atrial Fibrillation) subjects using EMD and Poincaré plot [33]. AF is described by the irregularity of RR intervals and the absence of the normal P wave which replaced by rapid oscillations [34]. The Poincaré plot of RR intervals is one of the techniques used in HRV analysis [35].

The technique consists of two steps: i) construction of multiscale series based on EMD (the preceding 9 IMFs); ii) construction of a Poincaré plot for the each of the scale. The data are from http://www.physionet.org/challenge/chaos/ [32].

Fig. 4 shows the area of the normal subject ellipse is smaller remarkably for scale1-4 and larger for scale7-9, comparing with AF subject in Fig.5. Both of them are more circular in small time scales than those in large time scales.

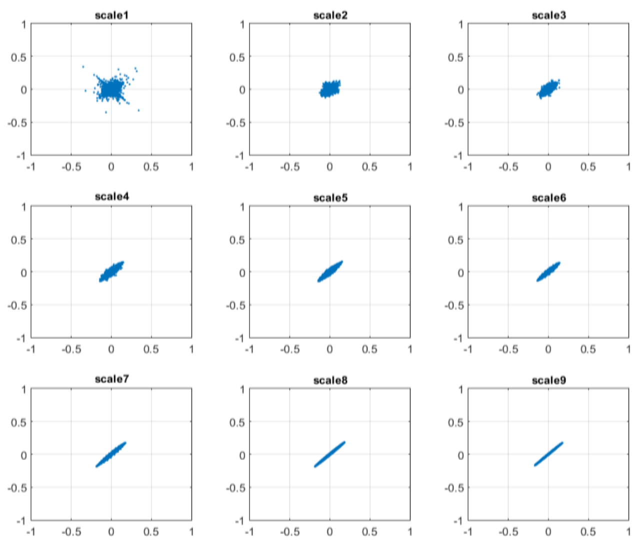

Fig. 4 Poincaré plots of each scale from normal subject RR intervals

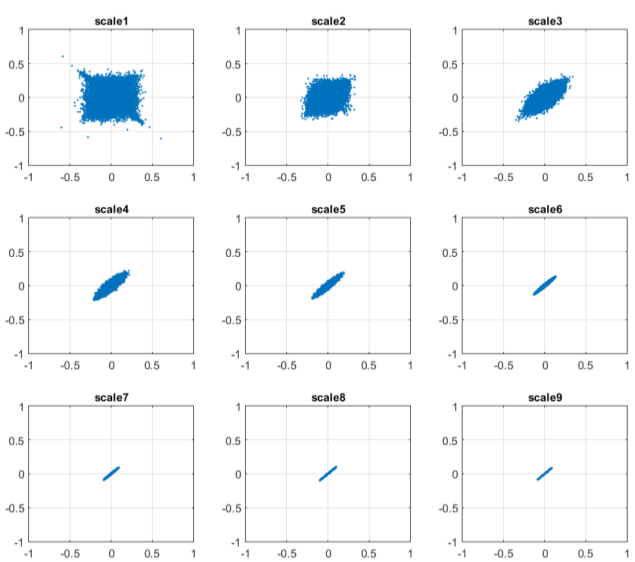

Fig. 5 Poincaré plots of each scale from AF subject RR intervals.

Besides, for larger time scales, the Poincaré plots show the classical elliptical shape indicative of long-range correlations [36].The differences between these data, which are not apparent from the original data or other conventional representations, support the potential utility of multiscale methods in exploring the dynamics of complex physiological system [37].

A basic multiscale phenomenon comes from the fact that signals often contain components at disparate scales. Different from other papers, we discussed multiscale phenomena and analysis in the perspective of data. And we choose physiological data as a developing platform to exhibit the good prospect of multiscale science.

IV. Conclusion and Prospects

The multiscale framework presented above is generic and can be applied in multi-disciplinary. Although some substantial progresses in multiscale science have already been achieved, this emerging field is still having a lot of space for further development [38].

Despite the exciting opportunity offered by multiscale science, specific scientific problems may be amenable to special methods. The greatest challenge encountered by multiscale science is the absence of a generalized norm widely accepted and many fundamental issues have to be addressed. Even though there is little doubt that multiscale science will play a major role in scientific issues, the challenges are quite daunting. These challenges include:

1) Accurate procedures for scale separation: Determining the scales to be included is the primary task of multiscale science. Scale separation dominates the subsequent modeling, as well as the form and strength of the coupling between scales.

2) The appropriate models for different scales: To connect different scales, we need to understand the basic formulation and properties of each scale. We cannot follow the same idea for different scales such as atomic structure and molecular dynamics. An overall comprehension of the system is helpful to select the appropriate models for each scale which can capture the physical behavior.

3) The relevance across scales: Understanding how scales are related to each other is to explore the cross-scale relevance. How to derive larger scales from detailed and smaller ones in the appropriate limit and how the cross-scale relevance transfers and affects the whole system are two open questions.

4) The errors due to multiscale modeling: When different models are matched together, a situation often encountered in practice is that there are large errors at the interface where the two models meet, and sometimes these errors can pollute a much larger part of the physical domain and even cause numerical instabilities [1]. This concern gains great importance in the context of solving complex multiscale problems where errors from each scale and the transfer among scales may impact the system performance in both subtle and obvious ways.

In conclusion, the overwhelming consensus is that the future progress of multiscale science is inseparable from the efforts of interdisciplinary cooperation. Growth in some vital areas, such as meteorology, nanotechnology, biotechnology and engineering, will be accelerated and catalyzed by the new multiscale methods. It is beyond the scope of this paper to fully pronounce on the multiscale science. However, based on current status, it is high time to open this debate and meet challenges. We believe that multiscale science has a bright future and a good application prospect.

ACKNOWLEDGMENT

This research was supported in part by the National Natural Science Foundation of China under grant No. 11272333 and No. 70871112.

REFERENCES

[1] E. Weinan, *Principles of multiscale modeling*, Cambridge University Press, 2011.

[2] D. Groen, S. J. Zasad, and P. V. Coveney, "Survey of Multiscale and Multiphysics Applications and Communities," *Comput. Sci. Eng.*, vol. 16, no. 2, pp. 34-43, March 2012.

[3] J. Glimm, and D. H. Sharp, "Multiscale science," *SIAM News*, October 1997.

[4] P. Colella, T. Hou, and L. Petzold, "Report of the first multiscale mathematics workshop: First steps toward a roadmap," *First DOE Workshop on Multiscale Mathematics in Modeling and Simulation*, *Alexandria Virginia*, May 2004.

[5] D. Estep, J. Shadid, and T. Simon, "Final Report Second DOE Workshop on Multiscale Problems," *Second DOE Workshop on Multiscale Mathematics, Broom-field Colorado*, July 2004.

[6] J. Dolbow, M. A. Khaleel, and J. Mitchell, "Multiscale Mathematics Initiative: A Roadmap," *Third DOE Workshop on Multiscale Mathematics*, December 2004.

[7] L. H. Chai, "Recent Progress of Multiscale Science," *Progress in Chemistry*, vol. 17, no. 2, pp. 186-191, 2005.

[8] B. L. Grigorenko, A. V. Rogov, I. A. Topol, S. K. Burt, H. M. Martinez, A. V. Nemukhin, et al, "Mechanism of the myosin catalyzed hydrolysis of ATP as rationalized by molecular modeling," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 104, no. 17, pp. 7057-61, April 2007.

[9] J. J. Koenderink, "The structure of images," *Biol. Cybern.*, vol. 50, no. 5, pp. 363-370, August 1984.

[10] I. Orlanski, "A rational subdivision of scales for atmospheric processes," *Bull. Am. Meteorol. Soc.,* vol. 56, pp. 527-530, 1975.

[11] M. Jebahi, F. Dau, J. L. Charles, and I. Iordanoff, "Multiscale modeling of complex dynamic problems: an overview and recent developments," *Arch. Comput. Method. E.*, vol. 23, no. 1, pp. 101-138, March 2016.

[12] S. Izvekov, and G. A. Voth, "A multiscale coarse-graining method for biomolecular systems," *J. Phys. Chem. B.*, vol. 109, no. 7, pp. 2469-73, February 2005.

[13] D. Porter, "Modelling of structural materials," *Int. Mater. Rev.*, vol. 47, no. 5, pp. 225-232, October 2002.

[14] D. J. Bacon, and Y. N. Osetsky, "Modelling atomic scale radiation damage processes and effects in metals," *Int. Mater. Rev.*, vol. 47, no. 5, pp. 233-241, October 2002.

[15] J. Pan, "Modelling sintering at different length scales," *Int. Mater. Rev.*, vol. 48, no. 2, pp. 69-85, April 2003.

[16] H. M. Zbib, D. H. Lassila, L. E. Levine, and K. J. Hemker, "Multiscale phenomena in materials — experiments and modeling related to mechanical behavior," *Materials Research Society Symposium*, *San Francisco, California, U.S.A*, April 2003.

[17] National Research Council, *Computational and Theoretical Techniques for Materials Science*, Washington, DC: The National Academies Press, 1995.

[18] J. A. Elliott, "Novel approaches to multiscale modelling in materials science," *Int. Mater. Rev.*, vol. 56, no. 4, pp. 207-225, July 2011.

[19] J. O. Dada, and P. Mendes, "Multi-scale modelling and simulation in systems biology," *Integr. Biol.*, vol. 3, no. 2, pp. 86-96, 2011.

[20] S. Schnell, R. Grima, and P. K. Maini, "Multiscale Modeling in Biology," *Am. Sci.*, vol. 95, no. 2, pp. 134-142, March 2007.

[21] J. Southern, J. Pitt-Francis, J. Whiteley, D. Stokeley, H. Kobashi, R. Nobes, et al, "Multi-scale computational modelling in biology and physiology," *Prog. Biophys. Mol. Biol.*, vol. 96, no. 1, pp. 60-89, April 2008.

[22] D. C. Walker, and J. Southgate, "The virtual cell—a candidate co-ordinator for 'middle-out' modelling of biological systems," *Brief. Bioinformatics.*, vol. 10, no. 4, pp. 450-461, March 2009.

[23] F. Verhein, and S. Chawla, "Mining spatio-temporal patterns in object mobility databases," *Data. Min. Knowl. Discov.*, vol. 16, no. 1, pp.5-38, February 2008.

[24] C. Jiang, P. Shang, and W. Shi, "Multiscale multifractal time irreversibility analysis of stock markets," *Physica. A.*, vol. 462, pp. 492-507, November 2016.

[25] C. Zhang, Z. Ni, and L. Ni, "Asymmetric multiscale behavior in PM2.5 time series: Based on asymmetric MS-DFA," *Physica. A.*, vol. 461, pp.355-365, November 2016.

[26] N. E. Huang, Z. Shen, S. R. Long, M. C. Wu, H. H. Shih, Q. Zheng, et al, "The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis," *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, vol. 454, no. 1971, pp. 903-995, The Royal Society, March 1998.

[27] J. Li, J. Zhang, W. Ge, and X. Liu, "Multi-scale methodology for complex systems," *Chem. Eng. Sci.*, vol. 59, no. 8, pp. 1687-1700, May 2004.

[28] D. Noble, "Modeling the heart—from genes to cells to the whole organ," *Science*, vol. 295, no. 5560, pp. 1678, March 2002.

[29] M. Costa, A. L. Goldberger, and C. K. Peng, "Multiscale entropy analysis of complex physiologic time series," *Phys. Rev. Lett.*, vol. 89, no. 6, pp. 068102, July 2002.

[30] U. R. Acharya, H. Fujita, V.K. Sudarshan, S. L. Oh, A. Muhammad, J. E. Koh, et al, "Application of empirical mode decomposition (EMD) for automated identification of congestive heart failure using heart rate signals," *Neural. Comput. Appl.,* pp. 1-22, 2016.

[31] M. G. Khan, *Rapid ECG interpretation*, 3rd ed., Springer Science & Business Media, 2008.

[32] A.L. Goldberger, L. A. Amaral, L. Glass, J.M Hausdorff, P. C. Ivanov, R. G. Mark, et al, "PhysioBank, PhysioToolkit, and PhysioNet: Components of a New Research Resource for Complex Physiologic Signals," *Circulation*, vol. 101, no. 23, e215-e220, June 2000.

[33] M. Brennan, M. Palaniswami, and P. Kamen, "Do existing measures of Poincare plot geometry reflect nonlinear features of heart rate variability?," *IEEE Trans Biomed. Eng.*, vol. 48, no. 11, pp. 1342-1347, November 2001.

[34] V. Fuster, L. E. Rydén, D. S. Cannom, H. J. Crijns, A. B. Curtis, K. A. Ellenbogen, et al, "ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines," *J. Am. Coll. Cardiol.*, vol. 48, no. 4, pp. 257-354, August 2006.

[35] J. Piskorski, and P. Guzik, "Geometry of the Poincare plot of RR intervals and its asymmetry in healthy adults," *Physiol. Meas.*, vol. 28, no. 3, pp. 287-300, February 2007.

[36] J. Hayano, F. Yamasaki, S. Sakata, A. Okada, S. Mukai, and T. Fujinami, "Spectral characteristics of ventricular response to atrial fibrillation," *Am. J. Physiol.*, vol. 273, no. 2, pp. 2811-6, December 1997.

[37] T. S. Henriques, S. Mariani, A. Burykin, F. Rodrigues, T. F. Silva, and A. L. Goldberger, "Multiscale Poincaré plots for visualizing the structure of heartbeat time series," *BMC Med. Inform. Decis. Mak.*, vol. 16, no. 1, pp. 17, February 2016.

[38] D. G. Vlachos, "A review of multiscale analysis: examples from systems biology, materials engineering, and other fluid–surface interacting systems," *Adv. Chem. Eng.*, vol. 30, pp. 1-61, December 2005.