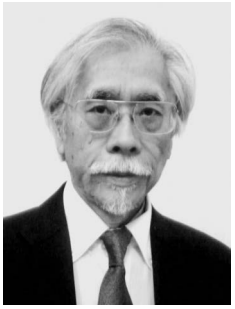
Japan Academy Prize to:

Toshiaki HISADA
Emeritus Professor,
The University of Tokyo
Chairman and CEO, UT-Heart Inc.

and

Seiryo SUGIURA
Emeritus Professor,
The University of Tokyo
President, UT-Heart Inc.



for "Multiscale–Multiphysics Simulation of the Human Heart and its Application to Medicine" (Joint Research)

Outline of the work:

This is a collaborative research on medical-engineering that was conducted intensively using the K computer. Dr. Toshiaki Hisada (Computational Mechanics) and Dr. Seiryo Sugiura (Medicine and Engineering) have developed the world's first cardiac simulator that mimics all electrochemical, physiological, and biomechanical functions of the heart, from the movement of contractile proteins to the pumping of blood. This has contributed to medical research by elucidating the electrical and mechanical functions of the heart, and has opened the door to a new medical field with clinical applications, such as predicting the effects of treatment by reproducing each patient's heart on a computer. Preparations for regulatory submission are underway.

Dr. Hisada has been working on continuum mechanics and finite element methods in the field of mechanical engineering for many years, especially on "large strain and large deformation problems" with strong nonlinearity and "coupled dynamics problems of flexible structures and fluids". In a paper published in 2001, he discovered a solution by using strongly coupled equations without distinguishing between fluid and structure, and established the theoretical basis for the heart simulation that was to be developed later.

Aside from being involved in the clinical treatment of heart disease, Dr. Sugiura has been studying cardiac mechanics at the organ level, which is directly related to the clinical symptoms of patients. He believes that the fundamental solution to heart disease can be achieved by combining his research with that at the molecular and cellular level. He has attempted to elucidate phenomena at various scales using single molecule physiology and an originally developed measurement system.

In 1998, the Graduate School of Frontier Sciences was established at the University of Tokyo,

and in 2002, the research and development of the heart simulator known as “UT-Heart” was started under the management of one laboratory with two professors (Dr. Hisada and Dr. Sugiura). Since 2003, they have promoted JST-CREST (Core Research for Evolutionary Science and Technology) research using the aforementioned fluid-structure interaction analysis method, and have succeeded in developing the world’s first multiphysics heart simulator. At the time of this project, the performance of computers was still insufficient, but they developed a multiscale analysis method that connects cells to organs via tissues. This later led to the achievements with the K computer. In 2008, they received the Commendation for Science and Technology from the Minister of Education, Culture, Sports, Science and Technology (MEXT) for this achievement. Furthermore, intensive R&D was continued under the JST Innovation Bridge Project from 2007, and the FIRST (Funding Program for World-Leading Innovative R&D on Science and Technology) program by the Cabinet Office (principal investigator: Dr. Ryozo Nagai) from 2010. The number of patent applications amounted to 169 (118 registrations). The K computer was completed in June 2012, but from its development stage, UT-Heart was selected as one of the RIKEN projects, and eventually became one of the seven priority programs selected by MEXT from all fields of science and technology. UT-Heart has been applied to basic and clinical medical research.

In basic research, they showed 1) the relationship between the transmural distribution of different cell types and the morphology of electrocardiogram, 2) the impact of fiber structure on the pumping performance, 3) a doubt on the functional significance of the cardiac looping, and 4) the importance of cooperative activation of cross-bridges on the pumping function. They also developed an in silico screening system for drug-induced arrhythmias using patch-clamp data on four ion channels.

On the other hand, as a result of clinical research, they have developed a method to recreate the heart of a patient on a computer based on the available hospital data. Once the heart of a patient is recreated on a computer, it is possible to apply various virtual treatments to it and predict in advance the one that will be most effective. They have been conducting clinical research on cardiac resynchronization therapy (CRT) and surgical procedures for pediatric congenital heart diseases. It is known from past statistical data that more than 30% of patients with CRT are non-responders, and if UT-Heart is approved by the pharmaceutical affairs bureau, it will be possible to avoid highly invasive surgery for non-responders by using advanced prediction instead.

In summary, (1) this research has greatly contributed to the development of computational science, (2) the heart reproduced on a computer can be effectively used for various researches, (3) this method of virtually predicting the best treatment in advance on a computer has extremely high clinical value, and (4) this method can be applied to organs other than the heart, opening the door to a new field of medicine (computer medicine).

They have also succeeded in developing new software that integrates molecular and cardiac simulations with amino acid level resolution, which will realize the simulation ranging from genes to the beating of the heart on Fugaku, the successor to the K computer, scheduled for completion in this fiscal year (2021).

List of Main Publications

1. Washio T, Sugiura S, Okada J and Hisada T. Using systolic local mechanical load to predict fiber orientation in ventricles. Front. Physiol. **11**, 467 (2020).
2. Kariya T, Washio T, Okada J, Nakagawa M, Watanabe M, Kadooka Y, Sano S, Nagai R, Sugiura S and Hisada T. Personalized Perioperative Multi-scale, multi-physics heart simulation of double outlet right ventricle. Ann. Biomed. Eng. **48**, 1740–1750 (2020).
3. Washio T, Shintani SA, Higuchi H, Sugiura S and Hisada T. Effect of myofibril passive elastic properties on the mechanical communication between motor proteins on adjacent sarcomeres. Sci. Rep. **9**, 9355 (2019).
4. Okada J, Yoshinaga T, Kurokawa J, Washio T, Furukawa T, Sawada K, Sugiura S and Hisada T. Arrhythmic hazard map for a 3D whole-ventricles model under multiple ion channel block. Br. J. Pharmacol. **175**, 3435–3452 (2018).
5. Washio T, Sugiura S, Kanada R, Okada J and Hisada T. Coupling langevin dynamics with continuum mechanics: Exposing the role of sarcomere stretch activation mechanisms to cardiac function. Front. Physiol. **9**, 333 (2018).
6. Okada J, Washio T, Nakagawa M, Watanabe M, Kadooka Y, Kariya T, Yamashita H, Yamada Y, Momomura S, Nagai R, Hisada T and Sugiura S. Absence of rapid propagation through the Purkinje network as a potential cause of line block in the human heart with left bundle branch block. Front. Physiol. **9**, 56 (2018).
7. Kaya M, Tani Y, Washio T, Hisada T and Higuchi H. Coordinated force generation of skeletal myosins in myofilaments through motor coupling. Nat. Commun. **8**, 16036 (2017).
8. Okada J, Washio T, Nakagawa M, Watanabe M, Kadooka Y, Kariya T, Yamada Y, Momomura S, Nagai R, Hisada T and Sugiura S. Multi-scale, tailor-made heart simulation can predict the effect of cardiac resynchronization therapy. J. Mol. Cell. Cardiol. **108**, 17–23 (2017)
9. Washio T, Hisada T, Shintani S and Higuchi H. Analysis of spontaneous oscillations for a three-state power-stroke model. Phys. Rev. E **95**, 022411 (2017)
10. Cui X, Washio T, Chono T, Baba H, Okada J-I, Sugiura S and Hisada T. Deformable regions of interest with multiple points for tissue tracking in echocardiography. Med. Image Anal. **35**, 554–555 (2017)
11. Panthee N, Okada J-I, Washio T, Mochizuki Y, Suzuki R, Koyama H, Ono M, Hisada T and Sugiura S. Tailor-made heart simulation predicts the effect of cardiac resynchronization therapy in a canine model of heart failure. Med. Image Anal. **31**, 46–62 (2016).
12. Zhang G, Chen X, Ohgi J, Miura T, Nakamoto A, Matsumura C, Sugiura S and Hisada T. Biomechanical simulation of thorax deformation using finite element approach. BioMed. Eng. OnLine **15**, 18 (2016).
13. Washio T, Yoneda K, Okada J-I, Kariya T, Sugiura S and Hisada T. Ventricualr fiber optimization utilizing the branching structure. Int. J. Numer. Method. Biomed. Eng. **32**, e02753 (2015).
14. Sugi S, Chaen S, Akimoto T, Minoda H, Miyakawa T, Miyauchi Y, Tanokura M and Sugiura S. Electron microscopic recording of myosin head power stroke in hydrated myosin filaments. Sci. Rep. **5**, 15700 (2015).

15. Hatano A, Okada J-I, Washio T, Hisada T and Sugiura S. An integrated finite element simulation of cardiomyocyte function based on triphasic theory. Front. Physiol. **6**, 287 (2015).
16. Yasuda C, Yasuda S, Yamashita H, Okada J, Hisada T and Sugiura S. hERG current inhibition selectively prolongs action potential of midmyocardial cells to augment transmural dispersion. J. Physiol. Pharmacol. **66**, 599–607 (2015).
17. Hatano A, Okada J-I, Washio T, Hisada T and Sugiura S. Distinct functional roles of cardiac mitochondrial subpopulations revealed by 3D simulation model. Biophys. J. **108**, 2732–2739 (2015).
18. Okada J, Yoshinaga T, Kurokawa J, Washio T, Furukawa T, Sawada K, Sugiura S and Hisada T. Screening system for drug-induced arrhythmogenic risk combining a patch clamp and heart simulator. Sci. Adv. **1**, e1400142 (2015).
19. Seo, K, Inagaki M, Hidaka I, Fukano H, Sugimachi M, Hisada T, Nishimura S and Sugiura S. Relevance of cardiomyocyte mechano-electric coupling to stretch-induced arrhythmias: optical voltage/calcium measurement in mechanically stimulated cells, tissues and organs. Prog. Biophys. Mol. Biol. **175**, 129–139 (2014).
20. Sugi H, Chaen S, Kobayashi T, Abe T, Kimura K, Saeki Y, Ohnuki Y, Miyakawa T, Tanokura M and Sugiura S. Definite differences between in vitro actin-myosin sliding and muscle contraction as revealed using antibodies to myosin head. PLOS ONE **9**, e93272 (2014).
21. Washio T, Okada J, Takahashi A, Yoneda K, Kadooka Y, Sugiura S and Hisada T. Multiscale heart simulation with cooperative stochastic cross-bridge dynamics and cellular structures. Multiscale Model. Simul. **11**, 965–999 (2013).
22. Okada J, Sugiura S and Hisada T. Modeling for cardiac excitation propagation based on the Nernst–Planck equation and homogenization. Phys. Rev. E **87**, 062701 (2013).
23. Hatano A, Okada J-I, Washio T, Hisada T and Sugiura S. Mitochondrial colocalization with Ca^{2+} release sites is crucial to cardiac metabolism. Biophys. J. **104**, 496–504 (2013).
24. Okada J, Sasaki T, Washio T, Yamashita H, Kariya T, Imai Y, Nakagawa M, Kadooka Y, Nagai R, Hisada T and Sugiura S. Patient specific simulation of body surface ECG using the finite element method. Pacing Clin. Electrophysiol. **36**, 309–321 (2013).
25. Katayama S, Umetani N, Hisada T and Sugiura S. Bicuspid aortic valves undergo excessive strain during its opening: A simulation study. J. Thorac. Cardiovasc. Surg. **145**, 1570–1576 (2013).
26. Sugi H, Abe T, Kobayashi T, Chaen S, Ohnuki Y, Saeki Y and Sugiura S. Enhancement of force generated by individual myosin heads in skinned rabbit psoas muscle fibers at low ionic strength. PLOS ONE **8**, e63658 (2013).
27. Asayama M, Kurokawa J, Shirakawa K, Okuyama H, Kagawa T, Okada J, Sugiura S, Hisada T and Furukawa T. Effects of a hERG activator, ICA-105574, on electrophysiological properties of canine hearts. J. Pharmacol. Sci. **121**, 1–8 (2013).
28. Sugiura S, Washio T, Hatano A, Okada J, Watanabe H and Hisada T. Multi-scale simulations of cardiac electrophysiology and mechanics using the University of Tokyo heart simulator. Prog. Biophys. Mol. Biol. **110**, 380–389 (2012).
29. Washio T, Okada J, Sugiura S and Hisada T. Approximation for cooperative interactions of a spatially-detailed cardiac sarcomere model. Cell. Mol. Bioeng. **5**, 113–126 (2012).

30. Hatano A, Okada J, Hisada T and Sugiura S. Critical role of cardiac t-tubule system for the maintenance of contractile function revealed by a 3D integrated model of cardiomyocytes. J. Biomech. **45**, 815–823 (2012).
31. Hatano A, Okada J, Washio T, Hisada T and Sugiura S. A 3-D simulation model of cardiomyocyte integrating excitation-contraction coupling and metabolism. Biophys. J. **101**, 2601–2610 (2011).
32. Okada J, Washio T, Maehara A, Momomura S, Sugiura S and Hisada T. Transmural and apicobasal gradients in repolarization contribute to T-wave genesis in human surface ECG. Am. J. Physiol. **301**, H200–H208 (2011).
33. Washio T, Okada J and Hisada T. A parallel multilevel technique for solving the bidomain equation on a human heart with Purkinje fibers and a torso model. SIAM Rev. **52**, 717–743 (2010).
34. Seo K, Inagaki M, Nishimura S, Hidaka I, Sugimachi M, Hisada T and Sugiura S. Structural heterogeneity in the ventricular wall plays a significant role in the initiation of stretch-induced arrhythmias in perfused rabbit right ventricular tissues and whole heart preparations. Circ. Res. **106**, 176–184 (2010).
35. Chen X, Sunagawa K and Hisada T. Development of a finite element contact analysis algorithm for charged-hydrated soft tissues with large sliding. Int. J. Numer. Method. Eng. **78**, 483–504 (2009).
36. Nishimura1 S, Manabe I, Nagasaki M, Eto K, Yamashita1 H, Ohsugi M, Otsu M, Hara K, Sugiura S, Yoshimura K, Kadowaki T and Nagai R. $CD8^+$ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat. Med. **15**, 914–920 (2009).
37. Sugi H, Minoda H, Inayoshi Y, Yumoto F, Miyakawa T, Miyauchi Y, Tanokura M, Akimoto T, Kobayashi T, Chaen S and Sugiura S. Direct demonstration of the cross-bridge recovery stroke in muscle thick filaments in aqueous solution by using the hydration chamber. Proc. Natl. Acad. Sci. USA **105**, 17396–17401 (2008).
38. Katayama S, Umetani N, Sugiura S and Hisada T. The sinus of Valsalva relieves abnormal stress on aortic valve leaflets by facilitating smooth closure. J. Thorac. Cardiovasc. Surg. **136**, 1528–1535 (2008).
39. Watanabe H, Sugiura S and Hisada T. The looped heart does not save energy by maintaining the momentum of blood flowing in the ventricle. Am. J. Physiol. **294**, H2191–H2196 (2008).
40. Washio T, Okada J and Hisada T. A parallel multilevel technique for solving the bidomain equation on a human heart with Purkinje fibers and a torso model. SIAM J. Sci. Comput. **30**, 2855–2881 (2008).
41. Nishimura S, Manabe I, Nagasaki M, Hosoya Y, Yamashita H, Ohsugi M, Tobe K, Kadowaki T, Nagai R and Sugiura S. In vivo imaging revealed local cell dynamics in obese adipose tissue inflammation. J. Clin. Invest. **118**, 710–721 (2008).
42. Sawada T and Hisada T. Fluid-structure interaction analysis of the two-dimensional flag-in-wind problem by an interface-tracking ALE finite element method. Comput. Fluids **36**, 136–146 (2007).
43. Koshiba N, Ando J, Chen X and Hisada T. Multiphysics simulation of blood flow and LDL

transport in a porohyperelastic arterial wall model. J. Biomech. Eng. **129**, 374–385 (2007).
44. Chui C, Kobayashi E, Chen X, Hisada T and Sakuma I. Transversely isotropic properties of porcine liver tissue: experiments and constitutive modelling. Med. Biol. Eng. Comput. **45**, 99–106 (2007).
45. Nishimura S, Nishimura M, Hosoya Y, Fujita H, Katoh M, Yamashita H, Manabe I, Tobe K, Kadowaki T, Nagai R and Sugiura S. Adipogenesis in obesity requires close interplay between differentiating adipocytes, stromal cells and blood vessels. Diabetes **56**, 1517–1526 (2007).
46. Chen Y, Chen X and Hisada T. Non-linear finite element analysis of mechanical electrochemical phenomena in hydrated soft tissues based on triphasic theory. Int. J. Numer. Method. Eng. **65**, 147–173 (2006).
47. Sugiura S, Nishimura S, Yasuda S, Hosoya Y and Katoh K. Carbon fiber technique for the investigation of single cell mechanics in intact cardiac myocytes. Nat. Protoc. **3**, 1453–1457 (2006).
48. Nishimura S, Nagai S, Katoh M, Yamashita H, Saeki Y, Okada J-I, Hisada T, Nagai R and Sugiura S, Microtubules modulate the stiffness of cardiomyocytes against shear stress. Circ. Res. **98**, 81–87 (2006).
49. Okada J, Sugiura S, Nishimura S and Hisada T. 3D simulation of calcium waves and contraction in cardiomyocytes using the finite element method. Am. J. Physiol. **288**, C510–C522 (2005).
50. Washio T, Hisada T, Watanabe H and Tezduyar TE. A robust preconditioner for fluid-structure interaction problems. Comput. Methods Appl. Mech. Eng. **194**, 4027–4047 (2005).
51. Watanabe H, Sugiura S, Kafuku H and Hisada T. Multi-physics simulation of left ventricular filling dynamics using fluid-structure interaction finite element method. Biophys. J. **87**, 2074–2085 (2004).
52. Zhang Q and Hisada T. Studies of the strong coupling and weak coupling methods in FSI analysis. Int. J. Numer. Method. Eng. **60**, 2013–2029 (2004).
53. Zhang Q and Hisada T. Analysis of fluid-structure interaction problems with structural buckling and large domain changes by ALE finite element method. Comput. Methods Appl. Mech. Eng. **190**, 6341–6357 (2001).

In addition to the papers listed above, Dr. Hisada has published 115 papers and Dr. Sugiura has published 93 papers.