Introduction

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Kazuo Tanishita and Kimiko Yamamoto

Abstract

The vascular system maintains the homeostasis by coordinating various transport phenomena- momentum, mass and the heat transfer- in the circulatory system. To understand the integrated view of dynamic equilibrium state, we need all the conventional macroscopic engineering, cellular and molecular approach. The integrated view of vascular system at multiple scales based on the multi-disciplinary approaches is referred to as vascular engineering. The vascular engineering aims to construct an integrated view, which comprises analysis, synthesis and medical applications. This book focuses on these three aspects of vascular engineering.

Keywords

Vascular engineering • Transport phenomena • Vascular system • Integrated view • Multi-disciplinary approaches

1.1 What Is Vascular Engineering?

The heart supplies blood to the vascular system to provide essential substances (nutrients, oxygen, hormones) to tissue cells and to remove biological waste. The vascular system, which consists of arterial and venous conduits and peripheral beds, generates flow resistance, being the mechanical load due to the pumping function of the heart. Because cells are in the range of several tens of microns in size, the

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capillary vessels in the peripheral beds are of 6-μm diameter, to facilitate mass and heat transport between the bloodstream and cells. In contrast, the aortic vessel, at which the distribution of the bifurcating blood-vessel network begins, is almost 20 mm in diameter. Thus, the structure of blood vessels differs significantly depending on their position within the circulatory system. The wall of the large aortic vessel is characterized by large quantities of elastic fibers; in contrast, arterioles have thick walls composed of smooth muscle fibers.

Vascular blood flow mediates the transport of substances of various molecular sizes to maintain a state of dynamic equilibrium in the tissue. This function of the vascular system is mediated by a series of dynamic processes (Lee 2004). That is, the vascular system maintains homeostasis by coordinating various transport phenomena—momentum (blood flow), mass, and heat transfer—in the circulatory system. These transport phenomena are described most frequently using a conventional engineering approach based on macroscopic fluid and solid mechanics (Fung 1990, 1997, 2010; Pedley 1980; Caro et al. 1978; Fournier 2012; Probstein 1989; Berger et al. 1996). However, analysis at the cellular and molecular levels is necessary for detailed investigation of mass transport in tissue (Probstein 1989). Indeed, mass transport at the cellular and molecular levels is frequently the focus of studies in the fields of biology and medicine (Friedman 2008; Hall 2011; Kierszenbaum and Tres 2012; Alberts et al. 1983). Therefore, investigation of transport phenomena in the vascular system must be conducted at multiple scales, which is facilitated by the use of multi-disciplinary approaches, including engineering, biology, and medicine (De et al. 2015). The field into the vascular (circulatory) system at multiple scales based on multi-disciplinary approaches is referred to as vascular engineering. Thus, vascular engineering addresses the coordinated dynamics of vessel functions, whereas vascular biology deals with the coordinated state of vessel structure, as shown in Fig. 1.1

A multi-scale view of the vascular system includes a range of scales from the whole body to the level of the individual molecule, as shown in Fig. 1.2. Vascular biology (Hall 2011; Kierszenbaum and Tres 2012) deals primarily with the molecular and cellular scales, while vascular engineering aims to explore the dynamical process of vessel function at a wider range of scales. Cardiovascular physiology (Klabunde 2012) involves investigation of the structure and function of the

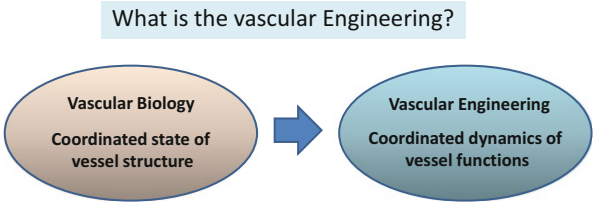

Fig. 1.1 The function of the vascular system is mediated by a series of dynamic processes. Vascular engineering involves investigation of the vascular system at multiple scales based on a multi-disciplinary approach. Thus, vascular engineering focuses on the coordinated dynamics of vessel functions, whereas vascular biology addresses the coordinated state of vessel structure

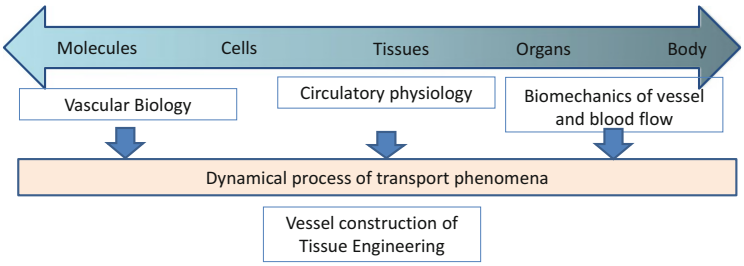

Fig. 1.2 The concept of vascular engineering involves the molecular to macroscopic scales and involves investigation of dynamic transport processes within the vascular system

cardiovascular network at a wide range of scales. Importantly, the detailed mechanical properties of the vascular system at scales larger than the capillaries can be investigated using fluid and solid mechanics together with mechanical analysis. Unfortunately, this macroscopic approach does not provide information on molecular-scale events; therefore, investigations at multiple scales are required to understand the roles of macro- and molecular-scale events in the vascular system.

In the vascular system, endothelial cells play an important role as the interface between mechanical and biological events (Davies 1995; Ando and Yamamoto 2011; Frangos 1993; Gefen 2011; Jacobs et al. 2012; Nagatomi 2011; Aranda-Espinoza 2015; Kiseleva and Kamkin 2010; Engler and Kumar 2014). Vascular endothelial cells—which comprise the inner lining of blood vessels—are exposed directly to the mechanical stimuli generated by blood flow and cyclic stretch due to left ventricle contraction. The response to these mechanical stimuli serves important homeostatic functions, including vascular remodeling. In other words, endothelial cells transduce mechanical signals into biochemical signals in the blood vessel. This phenomenon is designated mechano-transduction and is a rapidly growing area of interest in several fields (Kiseleva and Kamkin 2010; Engler and Kumar 2014).

One of the most difficult aspects of vascular engineering is achieving an integrated multi-scale view of events in the vascular system. Figure 1.3 illustrates the structural hierarchy of the vascular system at the molecular, organ, and whole-body scales; vascular engineering requires an integrated view of this hierarchical structure. Although the discipline necessary to fuse the molecular and macroscopic approaches is not yet available, vascular engineering aims to construct an integrated view of the multi-scale dynamic processes of the vascular system. The integrated view comprises analysis, synthesis, and medical applications (development of therapies). Modern biology, such as molecular biology, uses the analytical approach (Alberts 1983), whereas engineering uses the synthesis approach. The function of the vascular system can be understood using the synthesis approach, which is referred to as the constructive approach, by means of tissue engineering (Atala et al. 2008; Mofrad and Kamm 2009) and computer simulation (Rakocevic et al. 2013; Geris 2012). Both the analytical and synthesis approaches contribute to the construction of models of the vascular system; therefore, these approaches are

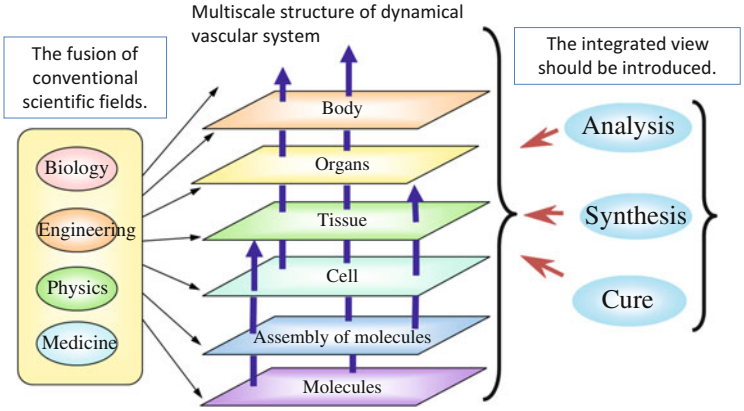

Fig. 1.3 Hierarchical structure of the vascular system at the molecular, organ and whole-body scales. Vascular engineering requires an integrated view of this hierarchical structure. This dynamic system can be understood only using a multi-scale and multi-disciplinary approach. Although the technology necessary to fuse the molecular and macroscopic approaches is not yet available, vascular engineering aims to construct an integrated view of the multi-scale dynamic processes of the vascular system. The integrated view comprises analysis, synthesis, and medical applications (development of therapies)

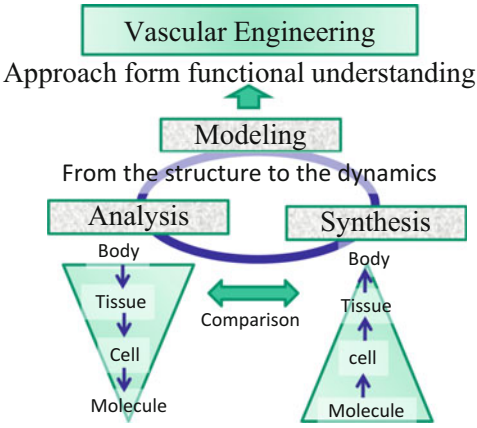

Fig. 1.4 Both analytical and synthesis approaches contribute to the construction of models of the vascular system; therefore, these approaches are utilized for medical applications (development of therapies)

utilized for medical applications (development of therapies), as shown in Fig. 1.4. The macroscopic view of the vascular system provides information on physico-chemical processes based on continuum mechanics, such as fluid and solid mechanics. Functional biological processes occur in the peripheral vascular network and at the cellular level in the tissue. Modern fields of biology, such as molecular biology, focus on the behavior of individual molecules, which are involved in maintaining the function of cells and tissues (Alberts 1983).

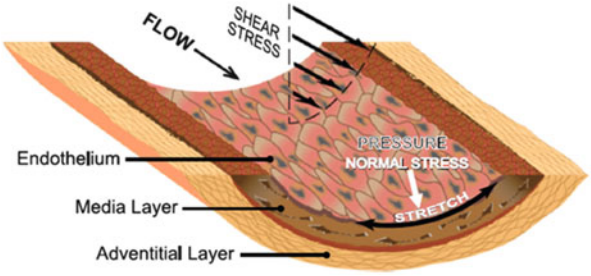

Fig. 1.5 The inner structure of an arterial blood vessel (Chiu and Chien (2011) The walls of arterial blood vessels consist of elastin, collagen and smooth muscle embedded in a mucopolysaccharide ground substance. Arterial vessel walls consist of three layers. The mechanical effects of blood flow are mediated by two types of stress; namely tangential stress (shear stress) and normal stress (pressure)

Mathematical models of blood flow and the mechanical properties of blood vessels have been well established and documented (Lee (2004), Fung (1990, 1997, 2010), Pedley (1980)) based on fluid and solid mechanics. On the other hand, experimental measurements provide quantitative information on the biological processes that occur within blood vessels. For detailed investigation of how the blood flow is coordinated with the blood vessel, knowledge of the inner structure of arterial blood vessels is required, as shown in Fig. 1.5 (Geris 2012). Arterial blood vessels consist of elastin, collagen, and smooth muscle embedded in a mucopolysaccharide ground substance. The wall of arterial vessels consists of three layers. The innermost layer is the tunica intima, which comprises endothelial cells, connective tissue, and basement membrane. The next layer is the thick tunica media, which contains elastin, smooth muscle, and collagen. The outermost layer is the adventitia, which comprises stiff collagen fibers.

Blood flow induces mechanical effects in terms of two types of stress, namely tangential stress (shear stress) and normal stress (pressure). The magnitude of tangential stress is proportional to the viscosity of the blood and the velocity gradient; this is commonly referred to as Newton's law. Tangential stress affects endothelial cells, and this mechanical stimulus has many biological and functional consequences that influence vessel dynamics. In contrast, pressure gives rise to cyclic stretch in vessel walls, which influences multiple biological processes. Furthermore, the various hemodynamic forces induce endothelial dysfunction by unfavorably moderating EC signaling and gene expression, resulting in the development of vascular pathologies (Chiu and Chien 2011).

1.2 Book Contents (Fig. 1.6)

This book focuses on three aspects of vascular engineering (Fig. 1.6); namely, analysis, synthesis, and medical applications (development of therapies). The contribution of each of these to the concept of vascular engineering is discussed.

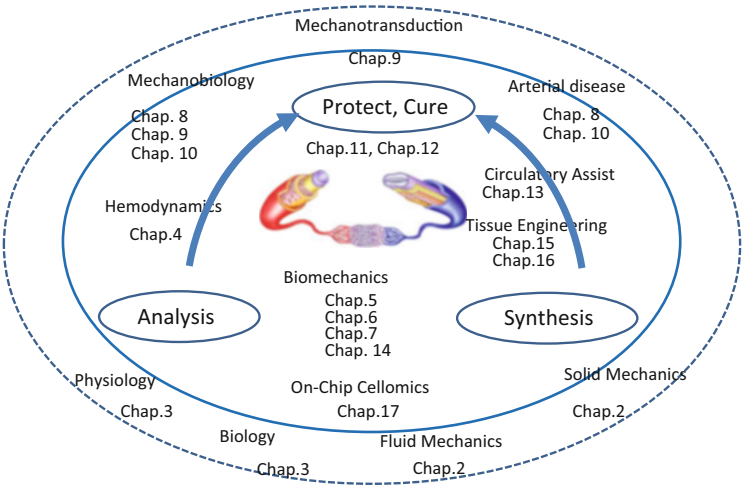

Fig. 1.6 This book focuses on three major aspects of blood vessel and flow dynamics

Chapter 2 deals with the mechanical viewpoint, which provides the basis for understanding various physiological and pathophysiological phenomena. The fundamentals of fluid and solid mechanics in relation to the circulatory system are introduced. In the first part, focusing on fluid mechanics, the concepts of Newtonian and non-Newtonian fluids are described. The rheological properties of blood are described and the universal mechanical law for flow through cylindrical tubes is explained. Based on this law, the characteristics of tube flow for Newtonian and non-Newtonian fluids are described and several mathematical models of blood flow through vessels presented. These models are closely related to important physiological phenomena. In the second part, the concept of continuum mechanics for a large deformation of the vascular wall is first discussed. Then, we introduce passive hyperelastic models, an active smooth muscle model, and discuss incorporation of residual strain and smooth muscle contractions. We demonstrate typical axisymmetric solutions of arterial wall stress for a tube model under physiological loading conditions; i.e., longitudinal stretch and intraluminal pressure. We also present several approaches for arterial diseases, such as atherosclerosis, aortic aneurysm, and dissection.

In Chap. 3, Dr. Aoki describes the basic mechanisms of homeostatic control in the cardiovascular system from the biological, physiological, and pathological point of view. How hemodynamic forces, hormones, cytokines, and neurotransmitters affect the control of vascular functions are stated at both the cellular and molecular levels. The mechanisms of some of the pathological conditions that develop from the breakdown of the proper regulation of the cardiovascular system, such as circulatory shock, hypertension, heart failure, and coronary artery disease, are also stated. In particular, new insights regarding the molecular mechanisms controlling the development of vascular diseases causing cerebral hemorrhage or cardiac infarction, including atherosclerosis and aneurysm,

are described comparing the different influences from either hemodynamic forces or chemical stimuli.

In Chap. 4, hemodynamics, being a part of cardiovascular physiology, deals with the forces that drive the blood circulation in mammalian cardiovascular systems. Pressure generated in the heart propels blood through the system continuously. In this chapter, the concepts of basic hemodynamics, essential to the interpretation of arterial disease with regard to bio-fluid mechanics, are introduced. A study of hemodynamics contributes to a better understanding of clinical and pathological observations and, in connection with mathematical models, facilitates the development of new methods for diagnosis. In particular, hemodynamic factors, such as wall shear stress and oscillatory shear index, correlate substantially with the generation and progression of arterial disease, including intimal thickening and atherosclerosis. The main aim of this chapter was to introduce hemodynamic applications of mathematical modeling of fluid mechanics. Mathematical models of fluid mechanics are used to quantify hemodynamic factors and their relationship to vascular disease. The majority of cardiovascular diseases and disorders are related to systemic hemodynamic dysfunction.

In Chap. 5, Dr. Kaunas and Dr. Deguchi focus on the reorganization of stress fibers in endothelial cells (ECs) in response to cyclic stretch. Cyclic stretch is caused by blood pressure acting on vascular walls in a perpendicular fashion based on the pulsatile flow and elongates endothelial cells and smooth muscle cells to the circumferential direction of the vascular walls. Vascular ECs are cultured on elastic stretch chambers to apply cyclic stretch; cells are then elongated and oriented perpendicularly to the stretch with reorganization of the stress fibers. They discuss the details of the biological characteristics of stress fibers in the first section, with the roles and molecular mechanisms of stress fibers in the cyclic stretch–induced signal transduction described in the latter section.

In Chap. 6, Dr. Ohashi focuses on the mechanical characteristics of vascular ECs in response to fluid shear stress. Fluid shear stress arises in ECs when blood flow disturbs the vascular endothelium. Shear stress in the human aorta is 10–20 dynes/cm^2, whereas shear stress on the walls of veins is 1–6 dynes/cm^2 under physiological conditions. Since blood flow changes in a pulsatile manner with each heartbeat, shear stress also regularly changes. ECs covering the inner surface of blood vessels sense shear stress generated by flowing blood and transmit the signal into the interior of the cell, which evokes a cellular response. Here Dr. Ohashi introduces some topics of cellular responses and mechanical properties, which were measured using flow-loading devices developed by his group members.

Chapter 7 describes how artery walls change their dimensions and mechanical properties adaptively in response to mechanical stimulation. These responses are mediated by the vascular smooth muscle cells (VSMCs) in the tunica media, and so detailed knowledge of the mechanical environment of the VSMCs is indispensable for understanding the mechanism underlying the adaptation. In this chapter, we first introduce the experimental techniques used for tensile testing of tissues and cells at a microscopic scale, and review in detail the tensile properties of VSMCs, followed by those of elastin and collagen fibers. In contrast to elastin and collagen fibers,

which are simple, passive materials, VSMCs are living entities with highly complex mechanical properties. Their mechanical properties are reviewed from the viewpoints of smooth muscle contraction, anisotropy in cytoskeletal structure, and viscoelasticity.

Chapter 8 describes the formation of atherosclerosis in the arterial vessel. Atherosclerosis is a serious disease that causes cardiovascular diseases such as cerebral infarction and myocardial infarction. Endothelial injury is the first step in atherogenesis by inducing increases in production of chemoattractant protein and adhesion molecules to leukocytes. One of the key events in atherogenesis is the recruitment of blood leukocytes, especially monocytes, to proatherogenic vascular regions and their subsequent transmigration across endothelial cells. Interactions between leukocytes and endothelial cells involve multi-step processes, including rolling, adhesion, locomotion, and transmigration. Therefore, mechanics and dynamics of endothelial cells and monocytes are important matters to understand the whole process of atherogenesis. Thus, Chap. 8 shows and discusses the mechanobiology of endothelial cells related to the formation of arterial disease.

In Chap. 9, Dr. Butler describes details concerning the molecular mechanisms of the mechanotransduction of fluid shear stress in vascular ECs. When shear stress acts on ECs, it can be converted into biological signals through various membrane-associated molecules and transmitted into the cell interior. The EC response to shear stress is closely linked to the regulation of vascular tone, blood coagulation as well as fibrinolysis, angiogenesis, and vascular remodeling, and plays an important role in maintaining the homoeostasis of the circulatory system. Multiple downstream pathways are involved in shear stress signaling, and they lead to changes in gene expression through the activation of a variety of transcription factors, which results in alterations in EC functions. However, the mechanisms and sensors by which ECs initially recognize shear stress have yet to be identified. Here, Dr. Butler will describe the candidates for shear stress sensors. Understanding the shear stress mechanotransduction, pathways will provide methods of promoting vascular health while also predicting, diagnosing, treating, and preventing vascular disease.

Chapter 10 describes bio-transport in endothelial cells, taking into consideration the effect of shear stress. Arteriosclerosis occurs preferentially at the inner side of the curvature of blood vessels, where shear stress induced by blood flow is low. It has been reported that macromolecules accumulate in these regions. Endothelial cells line the inner surface of blood vessels. A variety of substances are transported from blood vessels to tissues through endothelial cells. Many functions of endothelial cells are known to be affected by fluid shear stress, and dysfunction of endothelial transport is thought to be related to arteriogenesis. Endothelial transport is divided into two main types: passive paracellular transport and active transcellular transport. In this chapter, we introduce these two endothelial transport processes and describe the effects on them in various shear stress conditions.

Chapter 11 describes blood coagulation associated with platelet function. Platelet aggregation occurs at sites of vascular injury due to the high shear rate, and platelet behavior is sensitive to blood flow, which represents a mechanism for maintenance of hemostasis. Thus blood coagulation and platelets play a crucial

role in the maintenance of homeostasis in the vascular system. The identity of the majority of major players and the details of their roles in hemostasis and thrombus formation are known, but in most cases only qualitatively. In future, quantitative biological experiments and new computer simulation technology will contribute to advancement of the novel field of vascular engineering.

Chapter 12 focuses on novel technology for application of blood-compatible surfaces to vascular grafts. Despite much effort in the past several decades, no artificial graft has provided a satisfactory patency rate following application to small-caliber vessels (less than 5-mm diameter) in clinical applications. Owing to thrombus formation at the acute stage and intimal thickening caused by compliance mismatch, the long-term patency of these small-caliber vascular grafts is disappointing. Endothelial cell seeding has been proposed to improve the blood compatibility of small-diameter vascular grafts by creating an inner lining with non-thrombogenic surface characteristics similar to those of native blood vessels. We review a surface modification technique that enables the production of consistent and firm endothelial cell linings for hybrid vascular grafts—ion beam implantation.

Chapter 13 describes the vascular engineering of circulatory assist devices. Particular emphasis is placed on recent progress in ventricular assist devices and cardiopulmonary bypass pumps. These important medical devices assist human circulation during either the chronic or the acute phase. Because these devices are derived from an industrial pump, a large number of studies have been conducted from not only medical but also industrial and engineering perspectives. In this chapter, current ventricular assist devices and cardiopulmonary bypass pumps, their specifications, their classifications, and methods for their design and evaluation are presented, including analysis of flow within the pump to optimize the geometry.

In Chap. 14, Dr. Bonakdar and Dr. Goldmann et al. introduce several specific methods for analyzing cellular and molecular responses for different types of mechanical forces, such as shear stress, stretch, adhesion, and pressure, which are applied to several kinds of adherent cells. They review the following different methods for either measuring mechanical properties or applying mechanical forces: (i) a nano-scale particle tracking system, (ii) a magnetic tweezer system, (iii) a rotation disc rheometer, (iv) a magnetic twisting cytometry with optical detection system, (v) a cell poking system, and (vi) a traction force microscopy system. The latter part deals with the response of smooth muscle cells to these systems.

In Chap. 15, Dr. Takahashi and Dr. Naruse discuss how vascular ECs and smooth muscle cells (SMCs) can sense mechanical forces, including stretch elongation or fluid shear stress, particularly vascular SMCs when cyclic stretch is applied by pulsatile blood flow and vasoconstriction. Cultured SMCs are perpendicularly oriented with response to the direction of stretch elongation through the activation Notch signaling. They also mention some of the possibilities for applying knowledge from mechanobiology into “mechano-medicine,” including regenerative medicine. The pathological conditions due to vascular mechanotransduction pathways, for instance, arteriosclerosis and in-stent restenosis are also described. Appropriate methods for inducing vasculogenesis have been recently developed

using three-dimensional culture of ECs and SMCs with extracellular matrix protein, helping to predict the prognosis of artery disease.

In Chap. 16, the authors describe the culture methods to construct microvascular networks as well as approaches to integrating capillary networks with 3D epithelial tissue-engineered constructs. First, culture models of microvascular networks, such as *in vitro* angiogenesis and vasculogenesis models, are introduced. Using these culture models, the roles of endothelial cells (ECs), such as endothelial tip, stalk, and phalanx cells, are demonstrated. Additionally, regulatory factors, including both biochemical and biophysical factors, are discussed in the context of 3D capillary formation, including the process of vascular development, growth, and maturation. Next, we focus on the use of microfluidics technologies for investigating capillary morphogenesis. Examples of 3D capillary formation assays with growth factor gradients and different extracellular matrix materials are described. Cocultures of ECs and the other cell types in microfluidic devices are also introduced to show the potential of microfluidic vascular formation models. The vascularization of constructed tissues is discussed from the viewpoints of horizontal and vertical approaches for combining capillary structures and epithelial tissues *in vitro*. Finally, the concept of integrated vascular engineering and future perspectives are discussed.

In Chap 17, Dr. Yasuda introduces the unique technology of "on-chip cellomics" combining on-chip technology with the cellomics one. The on-chip cellomics system was originally developed by his group for analyzing epigenetic and genetic information or for use in the drug screening and the regenerative medicine. He describes detailed information regarding the mathematical model of the basic ideas and the specific methods of their systems. The single cell behavior of neurons or cardiomyocytes was then analyzed in order to apply the system to drug screening or tissue regeneration.

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