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Application of chemical reaction engineering principles to 'body-on-a-chip' systems

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Abstract

The combination of cell culture models with microscale technology has fostered emergence of *in vitro* cell-based microphysiological models, also known as organ-on-a-chip systems. Body-on-a-chip systems, which are multi-organ systems on a chip to mimic physiological relations, enable recapitulation of organ-organ interactions and potentially whole-body response to drugs, as well as serve as models of diseases. Chemical reaction engineering principles can be applied to understanding complex reactions inside the cell or human body, which can be treated as a multi-reactor system. These systems use physiologically-based pharmacokinetic (PBPK) models to guide the development of microscale systems of the body where organs or tissues are represented by living cells or tissues, and integrated into body-on-a-chip systems. Here, we provide a brief overview on the concept of chemical reaction engineering and how its principles can be applied to understanding and predicting the behavior of body-on-a-chip systems.

Keywords

physiologically based pharmacokinetic modeling; Microphysiological systems; Body-on-a-Chip; Drug development

Keywords

Biomolecular Engineering; Bioengineering; Biochemicals; Biofuels; Food

1. Introduction

Jay Bailey was in the forefront of biochemical engineering beginning in the late 1970's advocating the application of chemical engineering principles to understand living cells. By

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applying those principles to a living cell and by taking advantage of the insights emerging from molecular biology, he demonstrated that we could rationally manipulate living systems to serve humankind, for example, gaining insights into the best methods to produce proteins from recombinant DNA or metabolically engineering microbes to perform desired chemical transformations.[1] His work integrated sophisticated mathematical analysis with an effective understanding of the underlying biology.

Here we apply a similar approach to understanding and predicting human response to exposure to drugs and chemicals. We build upon the development of physiologically based pharmacokinetic (PBPK) models, first championed by two chemical engineers, Robert Dedrick and Ken Bischoff.[2] We have extended that approach to build a physical model of a human (or animal) using a PBPK to guide development of a set of interconnected compartments with each compartment representing a particular organ or tissue.[3] Later we demonstrated that such a system could be constructed using the techniques of microfabrication to construct a “Body-on-a-Chip” (BOC).[4] By using the techniques of microfabrication, it is possible to construct at a modest cost human-based systems to test drugs efficiently.

For decades, drug innovation has relied on cell-based high-throughput screening and animal models to identify promising therapeutics for clinical trials. Yet the drug attrition rates at clinical trial stages are persistently high (>88%), especially for oncology drugs (95%).[5] The giant gap between preclinical prediction and clinical outcomes is rooted in the interspecies differences in genetics and physiology between the experimental animals and the human body, as well as the disconnection between animal models of diseases and human diseases. The low predictive values of preclinical models and thus high clinical attrition rates have driven up the development cost of a new drug to approximately $2.6 billion recently.[6] The prevalent use of animals in experiments also raises significant ethical concerns globally. Therefore, the field of drug development, including regulatory authorities, pharmaceutical, and chemical companies, are actively searching for alternative strategies. Microphysiological models including BOC systems have emerged and gained momentum in recent years as an innovative tool for drug development and disease modeling. With a large number of start-up companies (over 28) involved in these efforts, there are several types of microphysiological systems.[7] While not yet adopted by major pharmaceutical companies for their standard preclinical drug development program, almost all major pharmaceutical companies are exploring this technology. In this review, we first briefly discuss the concept of BOC systems and related technology and the necessity to develop mathematical platforms for BOC systems. We then discuss introducing chemical reaction engineering principles to biological systems and describe how to apply these principles to the design and interpretation of BOC systems to maximize their potential for drug development.

1.1 Concept of organ-on-a-chip and body-on-a-chip systems

Microphysiological systems (MPS) refer to “engineered microsystems that represent units of human organs, modeling both structure and function”, as defined by National Institutes of Health (NIH),[8] and include single organ-on-a-chip (OOC), multi-organ but not physiologically directed (MOC), and BOC systems. A driving hypothesis of the field is that

such microscale biomimetics of human organs could simulate human physiology and disease progression, and thus offer more accurate predictions of human responses to therapeutics, as well as provide mechanistic insights into human diseases, while significantly reducing drug development cost and animal usage.

MPS emerge at the convergence of advanced stem cell technologies, biomaterials, functionally realistic cell constructs, microfabrication, and microfluidics technologies,[9] and have evolved rapidly with the collective effort from academia, pharmaceutical, and chemical companies, and regulatory agencies. OOC of a specific organ (e.g. the intestines) aims to recreate essential tissue-level structure (e.g. intestinal villi and crypts) and functionality (e.g. absorption and metabolism of the intestines) in vitro. To do so, a gut model first requires a considerable collection of different organ-specific cells (e.g. enterocytes, goblet cells, enteroendocrine cells, Paneth cells, microfold cells, cup cells, and tuft cells etc. for intestines). For example, Costello et al. developed a three-dimensional gut model based on hydrogel scaffold, using different cell types such as enterocytes and fibroblasts, as well as some of gut microbes that are known to reside in the gut.[10] While early development primarily used animal cells due to easy access and handling and potential applications for veterinary medicine and comparison between in vitro systems and animal models, the current focus is on human cell-based models. The shift is driven by great interests in using them as “human surrogates” for drug testing, and is partially enabled by recent breakthroughs in human stem cell technologies. Human induced pluripotent stem cells (hiPSCs) have been derived from adult somatic cells,[11–13] and differentiated into a variety of specialized cell types, including hepatocytes,[14] cardiomyocytes,[15,16] neurons,[17,18] pancreatic cells,[19] lung and airway epithelial cells,[20] brain microvascular endothelial cells,[21] and intestinal cells[22]. Such technologies provide a potentially unlimited source of organ-specific human cells, and enable creation of patient-[23] and disease-specific[24–26] MPS models for fully personalized drug testing. Other key components of a single-organ OOC model include in vivo-like cell microenvironment that allows cells to survive and maintain their cell type-specific phenotypes, and tissue-level cell organization, which is the basis for tissue-level functions. A variety of innovative biomaterials that mimic native extracellular matrix (ECM) in both composition and microstructure provide a promising tool for recreating cellular niches *in vitro*.[27] The latest 3D cell culture techniques based on scaffolds,[28] organoid self-assembly,[29–32] or 3D bioprinting[33] have made remarkable progress in creating complex multicellular organization that emulates tissue structures. In addition, advanced 2D and 3D microfabrication technologies enable creation of microscale features in the cell surroundings, which can modulate cell phenotype, guide cell organization, or provide in situ sensing. Advanced microfluidics technologies give precise control of fluid transport and interconnection, which regulate the chemical microenvironment. All these technologies have led to exciting advances of MPS. Recent examples with demonstration of tissue-level functionality include on-chip models for heart,[34,35] liver,[28] lung,[36,37] skin,[38,39] intestine,[40] kidney proximal tubule[41] and glomerulus[42], blood brain barrier,[43] blood-retinal barrier,[44] female reproductive system,[45] and placenta.[46]

When designing these OOC systems, it is usually not realistic to recapitulate all aspects of the organs, including cell and ECM composition, the microenvironment, tissue structure, and physiological functions. It is thus important to identify and model the key components of the

target organ that are essential to the physiological function of the organ. For example, the liver plays important roles in drug chemical reactions within the body, such as detoxification, glucose metabolism, bile acid and albumin synthesis, and production of numerous hormones, while the main function of the lung is to oxygenate the bloodstream through gas exchange. It would be rational to consider specific enzyme activities as major components when designing the liver chip, whereas the surface area per unit volume would be an important component when designing the lung chip. The reader is referred to more discussion on design considerations for other single-organ OOC systems, including heart, kidney, gut, brain/BBB, skin, vasculature, and cancer.[47]

Multi-organ microphysiological systems model organ-organ interactions in addition to individual organ functionality. The interactions on chip are usually established through fluidic connections with single-pass or recirculating perfusion.[48] Cell metabolites and soluble ligands released from one organ can be transported through the perfusion medium and act on another organ module in the systems. An early proof-of-concept system with lung and liver models recapitulated liver metabolism-dependent naphthalene toxicity toward lung epithelial cells.[49] BOC systems are a type of multi-organ MPS that emphasize relevance to the human body. BOC often mimic the human body by maintaining many key physiological parameters (e.g. organ perfusion rate) in its design, as well as the circulating architecture. Due to their physiological relevance, BOC systems hold great potential for simulating human physiology and predicting human responses.

1.2 Need for mathematical platform for body-on-a-chip systems

Human cell-based BOC systems could be a paradigm-shifting technology for drug development. Yet to derive meaningful interpretation for clinical practice and get the maximum potential from a BOC system, mathematical models are needed to guide its design and interpret the results, due to the inevitable differences between BOCs and the human body.

The biggest difference is the scale. The aim for BOC development is obviously not to replicate a real human body, but to create a microscale model that simulates human physiology. How to best reflect what happens in vivo using a miniaturized representation is the central question in designing a BOC system. The corresponding relationship between a BOC system and the human body is defined by scaling rules. Appropriate scaling strategies are needed to ensure that essential mechanisms of cell responses and organ-organ interactions in the BOC models align with those in vivo, and the results from a BOC model have specific interpretation for drug development. For example, an overrepresented liver module in the system could accelerate metabolism and clearance of testing drugs, decrease drug exposure, and may mask potential drug toxicity towards other organs.

The second major difference comes from the gap between design and construction. It is not trivial, or at least not cost-effective, to physically build an in vitro microsystem that can match the physiological counterpart at all essential aspects. For instance, developing a common medium as the “blood surrogate” for a BOC system is always challenging.[48] Recirculating whole blood is not practical, in part, due to the destruction of whole cells during recirculation in most MPS. While most MPS have used a serum-containing medium,

serum is not chemically defined and contains compounds that can promote growth and interfere with cell differentiation. Serum-free, chemically defined media have been developed that contain necessary hormones, lipids, serum proteins, and nutrients to sustain a variety of cells in a mature phenotype for an extended period (e.g. 28 days).[50,51] The blood surrogate is partially replaced each day (about 30%) and has a relevant drug carrying capacity. The development of serum-free media with full chemical definition improves the reliability and reproducibility of MPS. While current developed formula support basic nutrient supply and waste removal, their oxygen transport capacities at the same perfusion rate differ from that of the blood. The liquid-to-cell ratios in currently published multi-organ microphysiological systems typically range from several to thousands-fold larger than the human physiological values.[48] Other parameters, such as blood residence time, surface area-to-volume ratio, and cell type ratio, are also often not at physiological levels in many OOC models. Such discrepancies affect the dynamics of drug transport, metabolism, and cell responses, if not the mechanisms. Mathematical models can be used to introduce compensation in the design and to make adjustment to interpret the results. In addition, wide individual variation exists in the human population that BOCs model. It is not realistic to create a BOC model for each individual. However, one can establish a mathematic model that describes the varying parameters and in vitro results of a BOC model, and derive personalized treatment plan (e.g. individualized drug dosing, not just based on age or weight) using that mathematical model combined with scaling rules.

In summary, due to the discrepancy between a realistic BOC model and the human body of an individual, there is urgent need for developing mathematical platform that can help BOC systems generate meaningful information for drug development. In the following sections, we will introduce chemical reaction engineering principles and to the design and interpretation of BOC systems.

2. Application of chemical reaction engineering principles to biological systems

2.1 Principles of chemical reaction engineering

Chemical reaction engineering deals with reactions occurring in chemical reactors. It is an engineering field that studies the rates and mechanisms of chemical reactions and the design of the reactors in which they take place.[52] Various phenomena are considered as important in the field of chemical reaction engineering, such as fluid dynamics, mass and heat transfer, and reaction kinetics. The primary purpose of chemical reaction engineering is optimization of chemical reactors, feed composition and operating conditions. Chemical reaction engineering principles were originally derived mainly for applications in petrochemical industries. However, general principles can be applied to various other systems where reaction and transport of chemical species are involved. In this section, we provide a brief introduction to the concept of chemical reaction engineering. Most readers of the AIChE Journal are very familiar with the principles of chemical reaction engineering. Readers who come from a different background will find several textbooks as useful resources.[52,53] Here we provide a very brief introduction to the basic concepts of mole balance and reactor design in the next paragraph.

Main principles of chemical reaction engineering are based on mole balance equations. The concept of mass conservation states that the following equation holds for an open or closed system.

$$\text{Accumulation} = \text{In} - \text{Out} + \text{Generation} - \text{Consumption} \quad (1)$$

This basic equation can be modified appropriately depending on the type of reactors that are being considered. A batch reactor is a closed reactor where reactants are loaded at the beginning of reaction and reactions are carried out without inflow or outflow. There are two major types of flow reactors; a continuous stirred-tank reactor and a plug flow reactor. In a continuous stirred tank reactor (CSTR), feed streams supply reactants continuously to the reactor, where complete mixing ensures homogeneous distribution of reactants and products inside the reactor. Once the steady-state is achieved, a constant composition of outflow stream is observed, which is theoretically the same as that inside the reactor. By combining the mole balance equation for a reactor and the reaction rate equation, one can define the relationship between the reactor volume or time, and concentrations of reactants and products. This knowledge can be used to optimize the reactor design or operating conditions such as feed flow rate and feed composition.

The basic design approaches described above can be further extended to more complex situations, for example combination of multiple reactors, or presence of multiple reactions occurring in a reactor. In this case, deriving mass balance equations for each component or each reactor involved results in a set of differential equations that need to be solved numerically. Mathematical software tools capable of solving differential equations can be used, such as MATLAB, or more professional software tools dedicated to reactor design and process engineering are also available, such as Aspen-HYSYS®.

2.2 Living cells can be described by the principles of chemical reaction engineering

In principle, biological systems can be considered as chemical reactors (a single reactor or combination of reactors) at various length and time scales. For example, inside a single cell, thousands of chemical reactions occur simultaneously, such as transcription of DNA, translation of RNA, modification of synthesized proteins, and generation of energy by internal respiration. These reactions are often coupled with transport phenomena, for example, RNA molecules transcribed from its source DNA are transported out of cell nucleus to cytoplasm, where they are translated into proteins. Synthesized proteins are further modified and transported to their designated locations, sometimes outside the cells. These aspects make it natural to consider a living cell as a ‘bioreactor’, where chemical reaction engineering principles can be applied.

The application of chemical engineering principles to understand and describe cellular systems is well known in the bioprocess engineering literature.[1,54] Single cells can be described mathematically using the principles of chemical reaction engineering, and their changes in physiology can be linked to changes in external parameters such as concentrations of nutrients, chemical signaling factors, and physical parameters such as pH,

temperature, and shear stress. Population models can be constructed from an ensemble of single cell models (a segregated model) or a non-segregated model, that is, all cells are presumed to be identical.[55,56]

This concept that a living cell is basically a chemical reactor can be extended further to biological systems of a wide range of length scale. Considering the fact that the human body has hierarchical structures, with appropriate simplification and segmentation, the part or the whole of the human body can be considered as a 'living reactor', with inputs and outputs, and reactions occurring inside. The 'living reactor' can refer to a part or the whole of an organism, ranging from a single molecule (DNA or protein) to cells, tissues, organs, and the whole body. Here, we will provide some illustrative examples of biological systems that can be modeled using principles of chemical reaction engineering, such as using PBPK modeling.

2.3 Physiologically-based pharmacokinetic (PBPK) models

Pharmacokinetics (PK) refers to the science of drug absorption, distribution, metabolism and elimination (ADME), or more specifically the quantification of those processes, leading to the understanding, interpretation and prediction of concentration--time profiles in blood and various organs.[57,58] Pharmacokinetic models are basically a mass balance on a substance in the body, treating the body as a 'reactor'. The complexity of a PK model can vary, depending on the characteristics and the behavior of a drug in the body. For example, the body can be treated as a single, well-mixed compartment, or a combination of two or more compartments – a rapidly perfused compartment and a slowly perfused compartment. Often drugs accumulate differently at different tissues due to their interaction with the tissue structure. Rather than assuming well-mixed condition within an organ or a tissue, heterogeneity can be introduced by segregating the tissue into separate compartments. Figure 1 shows the different types of PK models with varying complexity.

PK models are formulated by setting a mass balance equation for a substance in a given compartment. For example, a two-compartment model can be set up to describe the PK of an orally absorbed drug. Here, the first compartment represents the gut, and the second compartment represents the rest of the body. The mass balance on the first compartment, gut, can be set up as follows.

$$\frac{dA}{dt} = -k_a A \quad (2)$$

where A is the amount of drug remaining in the gut lumen, and k_a is the absorption rate constant, assuming the first-order absorption kinetics. The mass balance on the second compartment, the body, can be set up as follows.

$$V\frac{dC}{dt} = k_a A - CL \cdot C \quad (3)$$

where V is the distribution volume, CL is the rate constant for clearance from the body, and C is the concentration of a drug in the body. Solving these two equations, one can obtain the expression for C as a function of time and rate constants k_a and CL.

$$C(t) = \frac{D}{V}\left(\frac{k_a}{k_a - CL}\right)\left(e^{-CL \cdot t} - e^{-k_a t}\right) \quad (4)$$

where D is the initial dose amount of a drug. This simple example of an empirical, two-compartment model illustrates how the principle of mass balance can be used to describe the fate of a drug in the body, given enough information about the rate of absorption and clearance.

A more mechanistic basis can be added to a PK model by segregating the body into separate organs. Often termed physiologically-based pharmacokinetic (PBPK) models, separate compartments are assumed for different organs, which are connected with hypothetical blood flows mimicking the blood circulation in the body. Each compartment acts as a reactor, absorber, or holding tank. This model is based on physiological considerations, because physiological parameters such as organ size, blood flow rate, and tissue-plasma partition coefficients are derived from the physiological conditions of the human body.[59] Mass balance equations for each compartment are written, constituting a set of ordinary differential equations, which can be solved numerically. These balances can be written not only for the parental compound but also metabolites. This feature is often critical in drug evaluation. Since a PBPK modeling approach is based on the actual physiological anatomy, it has a more mechanistic basis than the empirical compartment models, and specific mechanism of action can be related to a specific organ site. On the other hand, being a more complex model, a PBPK model requires a larger number of parameters than simple compartment models. However, potentially the number of adjustable parameters in a PBPK model may be fewer than in a PK model. While anatomical parameters such as organ volumes and blood perfusion rates can be found more easily, parameters such as enzyme kinetic parameters and partition coefficients are generally more difficult to determine. These parameters are compound-specific, and often show inter-individual variation as well. Obtaining the actual values of these parameters can be challenging. Several methods have been proposed and used for estimation of these parameters,[60,61] but parameter fitting using time-concentration data is often required.[62] Several strategies for numerical fitting of parameters have been developed. The reader is referred to detailed discussions of statistical inference techniques[63,64], concepts for parameter correlation detection[65] and model based experimental design techniques[66] as approaches that can be used to achieve better parameter estimates for these types of models. A brief discussion is also included in the supplementary document that is available online.

2.4 Enzyme reactions

Enzymes are biological molecules, generally proteins, acting as catalysts. Enzymes act upon ‘substrates’ to generate ‘products’. Enzymes are responsible for most of the metabolic processes within the cell. The knowledge about the mechanism of enzyme reaction allow

one to develop equations describing the kinetics of enzyme reaction. The basic mechanism of how enzymes work consists of two major steps, 1) binding of an enzyme to a substrate, and 2) generation of products. By setting up rate equations for each step and combining them, one can derive Michaelis-Menten kinetic equation[1].

$$v = \frac{v_{max}[S]}{K_m + [S]} \quad (5)$$

, where v is the enzyme reaction rate, [S] is the substrate concentration, v_{max} and K_m are constants. There are enzymes with more complex mechanism of action, for example enzymes with multiple binding sites, or enzymes requiring co-factors. In this case reaction rate equation can be more complex.[1] The Michaelis-Menten kinetics can explain the saturation kinetics often observed with enzyme reactions, that is, when substrate concentration is high, the observed reaction rate becomes constant.

Knowledge of enzyme kinetics is important since it helps understand and predict how enzymes will behave in a living system, and as well as provide a way to control how enzymes work. The two major parameters of enzyme reaction kinetics, v_{max} and K_m, where v_{max} represents the maximum reaction rate that can be achieved at high substrate concentrations, and K_m represents the half-saturation constant where the reaction rate is half of the maximum rate.

In case an enzyme is encapsulated inside a matrix, transport of substrates and products in and out of matrix can be a limiting step. The relative efficiency of transport and reaction can be evaluated using Damköhler number, Da, which is formulated as follows,

$$\mathrm{Da} = \frac{v_m}{k_L[S_b]} \quad (6)$$

where v_m is the maximum reaction rate per unit surface area (moles/s cm^2), and k_L is a mass transfer coefficient (cm/s), and S_b is bulk concentration of substrate (mole/cm^3). Da essentially represents the ratio of maximum reaction velocity to the maximum rate of mass transfer, and a high Da implies that the mass transfer is the limiting step, and a low Da implies that the reaction is the limiting step. The maximum reaction rate per unit surface area, v_m, can be modulated by varying the amount of enzyme available on the surface. An enzyme can also be immobilized on a free surface. In this case, the rate of transport of substrate molecules to the surface determines the reaction rate, as follows,[54]

$$J_x = k_L([S_b] - [S_s]) = \frac{V_{\max}[S_s]}{K_m + [S_s]} \quad (7)$$

The knowledge about the important parameters related to the reaction kinetics of enzymes, such as v_{max} and K_m, and transport of molecules within the reactor, such as k_L, helps one to optimize reactor design and operating conditions.

3. Designing and analysis of more physiologically-relevant body-on-a-chip systems

3.1 Progress in physiologically-based BOC systems

Microphysiological systems have shown significant progress thanks to recent advances in biomaterials, microfabrication technology, and cell biology. The human body functions as a complex orchestration of multiple organs, and many diseases arise as the result of untuning of such interactions. For example, the metabolic syndrome, often manifested by hypertension, obesity, and hyperglycemia, is thought to progress by multiple causes including stress, unbalanced diet, and sedentary life style, and can lead to more serious diseases such as cardiovascular diseases or type 2 diabetes.[67] While modern medicine has been highly effective at addressing acute diseases with a relatively simple mechanism of progression, chronic diseases have been more difficult to cure, due to its complexity of pathophysiology and the lack of accurate model systems.

As OOC technology has demonstrated success in recapitulating the essential functions of individual organs, the next foreseeable step is to create a system of multiple organs in a physiological manner (Body-on-a-chip (BOC) systems). These platforms aim to capture the interactions between multiple organs, and allow the prediction of both drug efficacy on a target organ and potential toxicity or side effects on another organ [68,69]. Clearly, some organs interact more with other organs than others, and carries greater importance in developing body-on-a-chip systems. For example, the liver has been the central organ in developing body-on-a-chip systems, due to its importance in biotransformation and detoxification. The gut and the kidney have also been considered important, because of their roles in absorption and clearance, respectively. For example, Shintu et al., combined liver and kidney cell culture in a microfluidic device with metabolomic footprinting technique to characterize the organ toxicity of compounds such as ammonia and acetaminophen.[70] There are numerous other examples of body-on-a-chip systems with an aim of recapitulating the effect of liver metabolism on other organs.[68,69,71–76] The gut also affects other organs extensively, as orally taken substances are absorbed through the gut. Several body-on-a-chip systems for observing the drug absorption in the gut and subsequent action in other organs have been reported. Esch et al. used a body-on-a-chip to evaluate the absorption of orally taken nanoparticles and their effect on the liver.[77] Shim et al., reported a microfluidic chip with three-dimensional culture of gut cells to evaluate drug absorption.[78] Mahler et al. developed a body-on-a-chip system connected with a separate module representing the gut, to evaluate the gut absorption of acetaminophen and its subsequent action on other cells such as the liver and the lung.[79]

Since the gut and the liver are the first two organs that orally taken substances encounter before entering the systemic circulation, they exert a significant effect on the bioavailability of the substances, as well as generation of metabolites. The term “first-pass metabolism”

refers to the phenomenon where an orally administered drug is metabolized to a significant extent before reaching the systemic circulation.[80] Reproducing the first-pass metabolism requires co-culture of gut and liver cells. Using microfluidic system enables mimicking the anatomical layout of the gut and liver, where molecules are absorbed in the gut, and then transported to the liver for subsequent metabolism. Several body-on-a-chip systems have been developed with an aim of reproducing the first-pass metabolism by co-culturing gut and liver cells in a microfluidic device, where the gut and the liver are connected via a fluidic channel or exist in indirect contact separated by a membrane. Bricks et al. reported a microfluidic co-culture system of liver and intestine cells to evaluate the first-pass metabolism of omeprazole and phenacetin.[81] Choe et al. also reported a body-on-a-chip system with a similar concept, where gut and liver cells are co-cultured in a chip within separate compartments, where intestinal absorption and hepatic metabolism are designed to occur sequentially.[82] After administration of a model compound, apigenin, to the gut compartment, both the original compound and the metabolites of the original compound were detected in the liver compartment, verifying the presence of absorption and metabolic reaction occurring in the system.

One aspect of body-on-a-chip systems for reproducing the first-pass metabolism is providing a basis to estimate the pharmacokinetic parameters. Since the absorption in the gut and the metabolism in the liver can be basically considered as coupled phenomena of transport and reaction, there have been attempts to utilize body-on-a-chip systems with gut and liver cells as an *in vitro* platform for prediction of pharmacokinetic parameters. Obviously, construction of a pharmacokinetic model representing the body-on-a-chip system can help with the extraction of necessary parameters from the experimental measurements. Prot et al. developed a body-on-a-chip system with gut and liver cells, coupled the chip system with a mathematical model to estimate intrinsic *in vitro* parameters and predict *in vivo* parameters.[83] A parallel tube model was used to model the hepatic metabolism, and parameters such as drug availability and hepatic clearance were calculated and compared with *in vivo* values. In an approach with a similar purpose, a PK model representing the gut-liver chip was used to calculate the concentration profile of a model drug, acetaminophen, and its metabolites observed in the chip.[84] Construction of a PK model representing the gut-liver chip allowed the authors to test several different parameters describing the properties of the gut and the liver, and compare the obtained PK profile from the chip model with the PK profile observed in the human body. This type of activity gave the authors insight into how the gut-liver chip should be designed and operated to mimic the PK profile of a drug in the human body.

3.2 Design considerations for body-on-a-chip systems

Construction of a PBPK model representing a body-on-a-chip basically follows the process of constructing a human PBPK model. A set of mass balance equation is set up for each compartment in the body-on-a-chip. The volumetric flow rate of media perfused into each chamber is intended to mimic the blood flow rate, and the volume of each chamber is intended to mimic the organ volume. This is well summarized in several research articles[68,74] as well as review articles[59,85]. One of the advantages of coupling a PBPK model with a body-on-a-chip is that the PBPK model can function as a mathematical platform for extracting PK parameters,[83] or to optimize the design of body-on-a-chip to achieve more

physiologically realistic PK profile.[84] Being the mathematical counterpart of a body-on-a-chip system, coupling the two *in silico* and *in vitro* models can help improve both systems. For example, a PK model can be used to interpret the experimental results obtained from the body-on-a-chip, or a PK model can be used to optimize the design of a body-on-a-chip. On the other hand, a body-on-a-chip can be used to verify hypotheses derived from a mathematical PK model, as illustrated in Figure 2.

A mathematical framework for body-on-a-chip systems can be particularly useful, because design and scaling of a body-on-a-chip system is important for correctly reproducing the response of the chip to drugs. For example, when considering the first-pass metabolism of a drug, obviously the relative sizes of the gut and the liver would influence the concentration of the drug in the chip.[84] Since there are many parameters that need to be considered, designing a body-on-a-chip correctly is not an easy task, and currently there is no simple solution. For example, some of the important physiological parameters that need to be considered are cardiac output, flow rates, number of cells, cell-liquid ratios, residence times in each organ, and intrinsic reaction rates. Several researchers suggested general principles for designing body-on-a-chip systems. Allometric scaling approaches have been demonstrated, where the number of cells, cell surface area, and metabolic rates were considered to set the ratio between different organs.[86] In another approach, the residence times in each organ chamber were considered as the main criteria for determining the flow rates and sizes of each chamber in a body-on-a-chip.[4] Abaci and Shuler proposed a set of design criteria for developing body-on-a-chip systems.[87] Parameters pertaining to a body-on-a-chip can be calculated based on the ADME parameters. Principles often used in chemical engineering can be useful for scaling purposes as well. In fluid mechanics or reaction engineering, equations are often non-dimensionalized, and this use of dimensionless numbers often gives a more valuable insight into how the system operates. For example, we mentioned the Damköhler number, Da, when analyzing the transport and reactions involving enzymes encapsulated within a matrix. In a similar approach, the same Damköhler number can be used to characterize the chemical reaction rate within a CSTR (continuous stirred tank reactor).

$$\mathrm{Da} = \frac{-r_{A0}V}{F_{A0}} \quad (8)$$

, where r_{A0} is the initial reaction rate, V is the reactor volume, F_{A0} is the molar flow rate of reactants entering the reactor. This dimensionless number, Da, represents the ratio of a reaction rate to a convection rate, and its value will allow easy determination of whether the reactor is convection-limited or reaction-limited. Such use of dimensionless numbers helps gain insight into how a system operates, and may be useful when scaling the human body into a microscale body-on-a-chip system.

One difficulty with correctly designing a body-on-a-chip system is that it can depend largely on the cell source, as cells from different sources will exhibit different characteristics, even if they are meant to represent the same organ. For example, the HepG2 cell line, a widely

used cell line for representing the liver, often shows extremely low activity for certain metabolic enzymes. The design of a body-on-a-chip would change depending on whether the HepG2 cell line or primary hepatocytes with more authentic enzyme levels were used.

Other common chemical engineering principles could also be important when designing physiologically-based BOC systems. For example, mass or oxygen transfer within the chip could become a limiting factor for cells to grow and function. In particular, many recent organ-on-a-chip systems incorporate 3D forms of cell culture, often cells encapsulated within a hydrogel or extracellular matrix. This type of cell culture complicates the issue of mass transfer, since sometimes efficient transfer of essential molecules can be hindered. Controlling the transfer of gases (oxygen or carbon dioxide) in and out of the chip systems can also be an important factor that affects the systems. Enzyme activity within the system is also an important consideration. Often enzymes need to function inside the systems, either existing within the living cells or in forms of partially purified enzymes. These enzymes can sometimes be immobilized within the surface of the chip or encapsulated within a 3D matrix. Characterizing and maintaining the activity of enzymes within the device is important, and sometimes can be quite challenging.

4. Future perspectives

The field of BOC systems has advanced to a point that quite a few aspects of pharmacokinetics and pharmacodynamics can be recapitulated in vitro.[48] After the initial platform development, the field is moving forward rapidly focusing on biological fidelity and clinical validation. Extrapolating clinically relevant parameters is critical for BOC systems to prove their value for drug development. We believe combining experimental (BOC) and computational (mathematical modeling) approaches to integration of multiple interacting organ models within a BOC device or across platforms is a practical strategy to obtain a general perspective of a drug's safety and efficacy as well as extract clinically relevant parameters.

The combination of BOC systems with mathematical modeling could take different forms with varied levels of physical integration. Most current BOC systems consist compartments representing 2 to 4 organs, and typically recapitulate a few aspects of the drug ADME process, such as intestinal absorption and metabolism of oral drugs [82,88–91], hepatic metabolism and bioactivation,[49,68,69,71,84,92] bioaccumulation,[93] blood brain barrier penetration,[94] and renal drug clearance.[93,94] Highly integrated BOC systems that recapitulate major aspects of drug ADME process and provide access to drug toxicity and efficacy evaluation are challenging to construct, yet not impossible. Miller et al. has developed a 14-chamber BOC system representing 13 organs within a single chip on a pumpless platform.[95] The interconnection scheme of various organ models follows an in vitro PBPK model simplified from the human PBPK model, and the on-chip organ perfusion rates and organ size ratios were all kept physiological. Their work demonstrates the possibility to construct and maintain much more complex BOC systems. Edington et al. described a 10-organ MPS on a pneumatically driven microfluidic platform, which provides intra-organ mixing, systemic recirculation, and physiological flow distribution among organ models.[96] Different organ models were developed individually on a uniform transwell-style

format and plugged into the platform for inter-organ connections. Such a strategy, as also previously used by the Marx research group,[97] simplifies integration of various organ models of different forms (e.g. 3D or 2D) and from different sources, but it also makes it difficult to maintain on-chip organ size ratios and liquid-to-tissue ratios at close-to-physiological levels. For that, the authors constructed a device PBPK model that also considers cell types and numbers in each organ model and working media volume in the system. They applied the PBPK model to analyze the distribution kinetics data for a nonsteroidal anti-inflammatory drug, diclofenac (DCF) and its metabolites (e.g. 4-OH-DCF) after apical gut administration (mimicking oral administration), and derived pharmacokinetic parameters (e.g. DCF unbound intrinsic clearance ($CL_{int(u)}$), the fraction of conversion of DCF to 4-OH-DCF) through parameter fitting. This work set an example of coupling mathematical modeling and MPS systems for in vitro pharmacokinetic studies. It should be noted, though, that such quantitative biology pharmacology (QBP) modeling is based on a clear understanding of the underlying mechanisms of drug responses. When the on-chip inter-organ relationships, such as organ size ratios and liquid-to-tissue ratios, deviate from physiological levels, the governing biological mechanisms of drug responses may also shift in vitro vs. in vivo. More importantly, in some cases, unknown biological mechanisms that occur in vivo fail to manifest themselves in the in vitro model due to different exposure dose and other factors. These unknown mechanisms cannot be detected through the comparison of results between the in vitro experiments and in silico simulations using the corresponding PBPK model based on known mechanisms. Similar pros and cos also apply to other MPS with unphysiological inter-organ relationships, including those functionally coupled yet physically decoupled MPS systems, in which different organ models developed and used for testing in geographically distanced laboratories are “connected” by transporting medium effluent from one model to another in a physiological order,[94] as well as systems with on-chip analytical modules for viability and functional readouts[75] (e.g. muscular contractile force, neural or cardiac electrical activity) for toxicity and efficacy evaluation. Overall, a highly integrated, PBPK model-guided BOC system maximally retains the physiological relationships among organs, while a QBP modeling-coupled, distributed system has loose constraints on physiological relevance but more design flexibility and analytical capability. These two types of MPS can be complementary in obtaining precise prediction of human drug response and clinically relevant parameters.

We also expect to see a broader application of BOC systems to precision medicine, especially to orphan drug development for rare diseases. Although each rare disease affects less than 1 in 2000 people, there are estimated over 7000 rare diseases and over 95% of these diseases do not have any drug treatments. Challenges in orphan drug development include lack of good animal models and existing data, extremely low patient enrollment for clinical trials, and heterogeneity in disease progress and treatment outcomes. With more public health funds (e.g. NIH) investing into precision medicine initiatives, we believe personalized BOC systems built from patient samples are on the horizon and hold great potential to help both preclinical and clinical stage orphan drug development. An OOC system that models cardiac weakness of Barth syndrome, a rare disease due to mutation of TAZ gene, has been demonstrated using cardiac iPSCs generated from patients’ skin biopsies.[98] With advanced iPSC technologies, a whole BOC system that carries a patient’s

genotype can be expected in the near future. With limited and heterogeneous patient population for clinical trials, establishing mathematical models based on chemical reaction engineering principles is especially important for orphan drug development to guide BOC experiment design, interpret experiment data, and ultimately produce clinically meaningful parameters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Literature Cited

1. Bailey JE, Ollis DF. Biochemical Engineering Fundamentals. New York, NY: McGraw-Hill; 1977.
2. Bischoff KB, Dedrick RL, Zaharko DS, Longstreth JA. Methotrexate pharmacokinetics. Journal of pharmaceutical sciences. 1971;60(8):1128–1133. [PubMed: 5127083]
3. Sweeney LM, Shuler ML, Babish JG, Ghanem A. A cell culture analogue of rodent physiology: Application to naphthalene toxicology. Toxicology in vitro : an international journal published in association with BIBRA. 1995;9(3):307–316. [PubMed: 20650092]
4. Sin A, Chin KC, Jamil MF, Kostov Y, Rao G, Shuler ML. The design and fabrication of three-chamber microscale cell culture analog devices with integrated dissolved oxygen sensors. Biotechnology progress. 2004;20(1):338–345. [PubMed: 14763861]
5. America PRaMo. 2016 Biopharmaceutical Research Industry Profile. Washington, DC: PhRMA; 2016.
6. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of health economics. 2016;47:20–33. [PubMed: 26928437]
7. Zhang B, Radisic M. Organ-on-a-chip devices advance to market. Lab on a chip. 2017;17(14):2395–2420. [PubMed: 28617487]
8. NIH/NCATS. What are tissue chips, and why are they important? https://ncats.nih.gov/tissuechip/about/faq#chips, accessed on 2018/05/11.
9. Ahadian S, Civitarese R, Bannerman D, et al. Organ-On-A-Chip Platforms: A Convergence of Advanced Materials, Cells, and Microscale Technologies. Advanced healthcare materials. 2018;7(2).
10. Costello CM, Sorna RM, Goh YL, Cengic I, Jain NK, March JC. 3-D intestinal scaffolds for evaluating the therapeutic potential of probiotics. Mol Pharm. 2014;11(7):2030–2039. [PubMed: 24798584]
11. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861–872. [PubMed: 18035408]
12. Ting JP, Duncan JA, Lei Y. How the noninflammasome NLRs function in the innate immune system. Science. 2010;327(5963):286–290. [PubMed: 20075243]
13. Lowry WE, Richter L, Yachechko R, et al. Generation of human induced pluripotent stem cells from dermal fibroblasts. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(8):2883–2888. [PubMed: 18287077]
14. Si-Tayeb K, Noto FK, Nagaoka M, et al. Highly efficient generation of human hepatocyte-like cells from induced pluripotent stem cells. Hepatology. 2010;51(1):297–305. [PubMed: 19998274]
15. Zhang J, Wilson GF, Soerens AG, et al. Functional cardiomyocytes derived from human induced pluripotent stem cells. Circulation research. 2009;104(4):e30–41. [PubMed: 19213953]

16. Lian X, Hsiao C, Wilson G, et al. Robust cardiomyocyte differentiation from human pluripotent stem cells via temporal modulation of canonical Wnt signaling. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(27):E1848–1857. [PubMed: 22645348]
17. Karumbayaram S, Novitch BG, Patterson M, et al. Directed differentiation of human-induced pluripotent stem cells generates active motor neurons. Stem cells. 2009;27(4):806–811. [PubMed: 19350680]
18. Shi Y, Kirwan P, Livesey FJ. Directed differentiation of human pluripotent stem cells to cerebral cortex neurons and neural networks. Nature protocols. 2012;7(10):1836–1846. [PubMed: 22976355]
19. Zhang D, Jiang W, Liu M, et al. Highly efficient differentiation of human ES cells and iPS cells into mature pancreatic insulin-producing cells. Cell research. 2009;19(4):429–438. [PubMed: 19255591]
20. Huang SX, Islam MN, O'Neill J, et al. Efficient generation of lung and airway epithelial cells from human pluripotent stem cells. Nature biotechnology. 2014;32(1):84–91.
21. Lippmann ES, Azarin SM, Kay JE, et al. Derivation of blood-brain barrier endothelial cells from human pluripotent stem cells. Nature biotechnology. 2012;30(8):783–791.
22. Spence JR, Mayhew CN, Rankin SA, et al. Directed differentiation of human pluripotent stem cells into intestinal tissue in vitro. Nature. 2011;470(7332):105–109. [PubMed: 21151107]
23. Gu M, Shao NY, Sa S, et al. Patient-Specific iPSC-Derived Endothelial Cells Uncover Pathways that Protect against Pulmonary Hypertension in BMPR2 Mutation Carriers. Cell stem cell. 2017;20(4):490–504 e495. [PubMed: 28017794]
24. Park IH, Arora N, Huo H, et al. Disease-specific induced pluripotent stem cells. Cell. 2008;134(5): 877–886. [PubMed: 18691744]
25. Dimos JT, Rodolfa KT, Niakan KK, et al. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. Science. 2008;321(5893):1218–1221. [PubMed: 18669821]
26. Maehr R, Chen S, Snitow M, et al. Generation of pluripotent stem cells from patients with type 1 diabetes. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(37):15768–15773. [PubMed: 19720998]
27. Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science. 2017;356(6337).
28. Esch MB, Prot JM, Wang YI, et al. Multi-cellular 3D human primary liver cell culture elevates metabolic activity under fluidic flow. Lab on a chip. 2015;15(10):2269–2277. [PubMed: 25857666]
29. Lancaster MA, Renner M, Martin CA, et al. Cerebral organoids model human brain development and microcephaly. Nature. 2013;501(7467):373–379. [PubMed: 23995685]
30. Freedman BS, Brooks CR, Lam AQ, et al. Modelling kidney disease with CRISPR-mutant kidney organoids derived from human pluripotent epiblast spheroids. Nature communications. 2015;6:8715.
31. Takebe T, Zhang RR, Koike H, et al. Generation of a vascularized and functional human liver from an iPSC-derived organ bud transplant. Nature protocols. 2014;9(2):396–409. [PubMed: 24457331]
32. Chen YW, Huang SX, de Carvalho A, et al. A three-dimensional model of human lung development and disease from pluripotent stem cells. Nature cell biology. 2017;19(5):542–549. [PubMed: 28436965]
33. Zhang YS, Yue K, Aleman J, et al. 3D Bioprinting for Tissue and Organ Fabrication. Annals of biomedical engineering. 2017;45(1):148–163. [PubMed: 27126775]
34. Grosberg A, Alford PW, McCain ML, Parker KK. Ensembles of engineered cardiac tissues for physiological and pharmacological study: heart on a chip. Lab on a chip. 2011;11(24):4165–4173. [PubMed: 22072288]
35. McCain ML, Sheehy SP, Grosberg A, Goss JA, Parker KK. Recapitulating maladaptive, multiscale remodeling of failing myocardium on a chip. Proceedings of the National Academy of Sciences of the United States of America. 2013;110(24):9770–9775. [PubMed: 23716679]
36. Stucki AO, Stucki JD, Hall SR, et al. A lung-on-a-chip array with an integrated bio-inspired respiration mechanism. Lab on a chip. 2015;15(5):1302–1310. [PubMed: 25521475]

37. Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. Reconstituting organ-level lung functions on a chip. Science. 2010;328(5986):1662–1668. [PubMed: 20576885]
38. Abaci HE, Gledhill K, Guo Z, Christiano AM, Shuler ML. Pumpless microfluidic platform for drug testing on human skin equivalents. Lab on a chip. 2015;15(3):882–888. [PubMed: 25490891]
39. Abaci HE, Guo Z, Coffman A, et al. Human Skin Constructs with Spatially Controlled Vasculature Using Primary and iPSC-Derived Endothelial Cells. Advanced healthcare materials. 2016;5(14): 1800–1807. [PubMed: 27333469]
40. Bein A, Shin W, Jalili-Firoozinezhad S, et al. Microfluidic Organ-on-a-Chip Models of Human Intestine. Cellular and molecular gastroenterology and hepatology. 2018;5(4):659–668. [PubMed: 29713674]
41. Weber EJ, Chapron A, Chapron BD, et al. Development of a microphysiological model of human kidney proximal tubule function. Kidney international. 2016;90(3):627–637. [PubMed: 27521113]
42. Musah S, Mammoto A, Ferrante TC, et al. Mature induced-pluripotent-stem-cell-derived human podocytes reconstitute kidney glomerular-capillary-wall function on a chip. Nature biomedical engineering. 2017;1.
43. Wang YI, Abaci HE, Shuler ML. Microfluidic blood-brain barrier model provides in vivo-like barrier properties for drug permeability screening. Biotechnology and bioengineering. 2017;114(1):184–194. [PubMed: 27399645]
44. Yeste J, Garcia-Ramirez M, Illa X, et al. A compartmentalized microfluidic chip with crisscross microgrooves and electrophysiological electrodes for modeling the blood-retinal barrier. Lab on a chip. 2017;18(1):95–105. [PubMed: 29168876]
45. Xiao S, Coppeta JR, Rogers HB, et al. A microfluidic culture model of the human reproductive tract and 28-day menstrual cycle. Nature communications. 2017;8:14584.
46. Lee JS, Romero R, Han YM, et al. Placenta-on-a-chip: a novel platform to study the biology of the human placenta. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2016;29(7):1046–1054.
47. Ronaldson-Bouchard K, Vunjak-Novakovic G. Organs-on-a-Chip: A Fast Track for Engineered Human Tissues in Drug Development. Cell Stem Cell. 2018;22(3):310–324. [PubMed: 29499151]
48. Wang YI, Carmona C, Hickman JJ, Shuler ML. Multiorgan Microphysiological Systems for Drug Development: Strategies, Advances, and Challenges. Advanced healthcare materials. 2018;7(2).
49. Viravaidya K, Sin A, Shuler ML. Development of a microscale cell culture analog to probe naphthalene toxicity. Biotechnology progress. 2004;20(1):316–323. [PubMed: 14763858]
50. Wang YI, Oleaga C, Long CJ, et al. Self-contained, low-cost Body-on-a-Chip systems for drug development. Experimental biology and medicine. 2017;242(17):1701–1713. [PubMed: 29065797]
51. Schaffner AE, Barker JL, Stenger DA, Hickman JJ. Investigation of the factors necessary for growth of hippocampal neurons in a defined system. J Neurosci Methods. 1995;62(1–2):111–119. [PubMed: 8750092]
52. Fogler SH. Elements of Chemical Reaction Engineering. Prentice Hall; 2016.
53. Levenspiel O Chemical Reaction Engineering. Wiley; 1999.
54. Shuler ML, Kargi F, DeLisa M. Bioprocess Engineering: Basic Concepts. 3rd ed. Boston, Massachusetts: Prentice Hall; 2017.
55. Domach MM, Shuler ML. A finite representation model for an asynchronous culture of E. coli. Biotechnology and bioengineering. 1984;26(8):877–884. [PubMed: 18553472]
56. Domach MM, Leung SK, Cahn RE, Cocks GG, Shuler ML. Computer model for glucose-limited growth of a single cell of Escherichia coli B/r-A. Biotechnology and bioengineering. 1984;26(9): 1140.
57. Aarons L Physiologically based pharmacokinetic modelling: a sound mechanistic basis is needed. British journal of clinical pharmacology. 2005;60(6):581–583. [PubMed: 16305581]
58. Gerlowski LE, Jain RK. Physiologically based pharmacokinetic modeling: principles and applications. Journal of pharmaceutical sciences. 1983;72(10):1103–1127. [PubMed: 6358460]

59. Sung JH, Esch MB, Shuler ML. Integration of in silico and in vitro platforms for pharmacokinetic-pharmacodynamic modeling. Expert opinion on drug metabolism & toxicology. 2010;6(9):1063–1081. [PubMed: 20540627]
60. Schuhmann G, Fichtl B, Kurz H. Prediction of drug distribution in vivo on the basis of in vitro binding data. Biopharmaceutics & drug disposition. 1987;8(1):73–86. [PubMed: 3580515]
61. Iwatsubo T, Hirota N, Ooie T, et al. Prediction of in vivo drug metabolism in the human liver from in vitro metabolism data. Pharmacology & therapeutics. 1997;73(2):147–171. [PubMed: 9131722]
62. Kim DS, Sung JH, Lee JM. Robust parameter estimation for physiologically based pharmacokinetic model of Tegafur with dissolution dynamics. Chemical Engineering Research and Design. 2015;104:730–739.
63. Walter EP, Norton L , J. Identification of parametric models from experimental data. Springer Verlag; 1997.
64. Bates DM, Watts DG. Nonlinear regression analysis and its applications. John Wiles & Sons, Inc; 1988.
65. Li P, Vu QD. Identification of parameter correlations for parameter estimation in dynamic biological models. BMC systems biology. 2013;7:91. [PubMed: 24053643]
66. Franceschini G, Macchietto S. Anti-Correlation Approach to Model-Based Experiment Design: Application to a Biodiesel Production Process. Industrial & Engineering Chemistry Research. 2008;47(7):2331–2348.
67. Bergman RN. Orchestration of glucose homeostasis: from a small acorn to the California oak. Diabetes. 2007;56(6):1489–1501. [PubMed: 17526912]
68. Sung JH, Kam C, Shuler ML. A microfluidic device for a pharmacokinetic-pharmacodynamic (PK-PD) model on a chip. Lab on a chip. 2010;10(4):446–455. [PubMed: 20126684]
69. Sung JH, Shuler ML. A micro cell culture analog (microCCA) with 3-D hydrogel culture of multiple cell lines to assess metabolism-dependent cytotoxicity of anti-cancer drugs. Lab on a chip. 2009;9(10):1385–1394. [PubMed: 19417905]
70. Shintu L, Baudoin R, Navratil V, et al. Metabolomics-on-a-chip and predictive systems toxicology in microfluidic bioartificial organs. Analytical chemistry. 2012;84(4):1840–1848. [PubMed: 22242722]
71. Choucha-Snouber L, Aninat C, Grsicom L, et al. Investigation of ifosfamide nephrotoxicity induced in a liver-kidney co-culture biochip. Biotechnology and bioengineering. 2013;110(2):597–608. [PubMed: 22887128]
72. Lee J, Choi JR, Ha SK, et al. A microfluidic device for evaluating the dynamics of the metabolism-dependent antioxidant activity of nutrients. Lab on a chip. 2014;14(16):2948–2957. [PubMed: 24920301]
73. Vunjak-Novakovic G, Bhatia S, Chen C, Hirschi K. HeLiVa platform: integrated heart-liver-vascular systems for drug testing in human health and disease. Stem cell research & therapy. 2013;4 Suppl 1:S8. [PubMed: 24565063]
74. Tatosian DA, Shuler ML. A novel system for evaluation of drug mixtures for potential efficacy in treating multidrug resistant cancers. Biotechnology and bioengineering. 2009;103(1):187–198. [PubMed: 19137589]
75. Oleaga C, Bernabini C, Smith AS, et al. Multi-Organ toxicity demonstration in a functional human in vitro system composed of four organs. Scientific reports. 2016;6:20030. [PubMed: 26837601]
76. Oleaga C, Riu A, Rothemund S, et al. Investigation of the effect of hepatic metabolism on off-target cardiotoxicity in a multi-organ human-on-a-chip system. Biomaterials. 2018;182:176–190. [PubMed: 30130706]
77. Esch MB, Mahler GJ, Stokol T, Shuler ML. Body-on-a-chip simulation with gastrointestinal tract and liver tissues suggests that ingested nanoparticles have the potential to cause liver injury. Lab on a chip. 2014;14(16):3081–3092. [PubMed: 24970651]
78. Shim KY, Lee D, Han J, Nguyen NT, Park S, Sung JH. Microfluidic gut-on-a-chip with three-dimensional villi structure. Biomedical microdevices. 2017;19(2):37. [PubMed: 28451924]
79. Mahler GJ, Esch MB, Glahn RP, Shuler ML. Characterization of a gastrointestinal tract microscale cell culture analog used to predict drug toxicity. Biotechnology and bioengineering. 2009;104(1):193–205. [PubMed: 19418562]

80. Nakanishi T, Tamai I. Interaction of Drug or Food with Drug Transporters in Intestine and Liver. Current drug metabolism. 2015;16(9):753–764. [PubMed: 26630906]
81. Bricks T, Hamon J, Fleury MJ, et al. Investigation of omeprazole and phenacetin first-pass metabolism in humans using a microscale bioreactor and pharmacokinetic models. Biopharmaceutics & drug disposition. 2015;36(5):275–293. [PubMed: 25678106]
82. Choe A, Ha SK, Choi I, Choi N, Sung JH. Microfluidic Gut-liver chip for reproducing the first pass metabolism. Biomedical microdevices. 2017;19(1):4. [PubMed: 28074384]
83. Prot JM, Maciel L, Bricks T, et al. First pass intestinal and liver metabolism of paracetamol in a microfluidic platform coupled with a mathematical modeling as a means of evaluating ADME processes in humans. Biotechnology and bioengineering. 2014;111(10):2027–2040. [PubMed: 24954399]
84. Lee DW, Ha SK, Choi I, Sung JH. 3D gut-liver chip with a PK model for prediction of first-pass metabolism. Biomedical microdevices. 2017;19(4):100. [PubMed: 29116458]
85. Sung JH, Srinivasan B, Esch MB, et al. Using physiologically-based pharmacokinetic-guided “body-on-a-chip” systems to predict mammalian response to drug and chemical exposure. Experimental biology and medicine. 2014;239(9):1225–1239. [PubMed: 24951471]
86. Moraes C, Labuz JM, Leung BM, Inoue M, Chun TH, Takayama S. On being the right size: scaling effects in designing a human-on-a-chip. Integrative biology : quantitative biosciences from nano to macro. 2013;5(9):1149–1161. [PubMed: 23925524]
87. Abaci HE, Shuler ML. Human-on-a-chip design strategies and principles for physiologically based pharmacokinetics/pharmacodynamics modeling. Integrative biology : quantitative biosciences from nano to macro. 2015;7(4):383–391. [PubMed: 25739725]
88. Kimura H, Ikeda T, Nakayama H, Sakai Y, Fujii T. An on-chip small intestine-liver model for pharmacokinetic studies. Journal of laboratory automation. 2015;20(3):265–273. [PubMed: 25385717]
89. van Midwoud PM, Groothuis GM, Merema MT, Verpoorte E. Microfluidic biochip for the perifusion of precision-cut rat liver slices for metabolism and toxicology studies. Biotechnology and bioengineering. 2010;105(1):184–194. [PubMed: 19718695]
90. Imura Y, Sato K, Yoshimura E. Micro total bioassay system for ingested substances: assessment of intestinal absorption, hepatic metabolism, and bioactivity. Analytical chemistry. 2010;82(24): 9983–9988. [PubMed: 21090751]
91. Imura Y, Yoshimura E, Sato K. Micro total bioassay system for oral drugs: evaluation of gastrointestinal degradation, intestinal absorption, hepatic metabolism, and bioactivity. Analytical sciences : the international journal of the Japan Society for Analytical Chemistry. 2012;28(3):197–199. [PubMed: 22451356]
92. Zhang YS, Aleman J, Shin SR, et al. Multisensor-integrated organs-on-chips platform for automated and continual in situ monitoring of organoid behaviors. Proceedings of the National Academy of Sciences of the United States of America. 2017;114(12):E2293–E2302. [PubMed: 28265064]
93. An F, Qu Y, Luo Y, et al. A Laminated Microfluidic Device for Comprehensive Preclinical Testing in the Drug ADME Process. Scientific reports. 2016;6:25022. [PubMed: 27122192]
94. Vernetti L, Gough A, Baetz N, et al. Functional Coupling of Human Microphysiology Systems: Intestine, Liver, Kidney Proximal Tubule, Blood-Brain Barrier and Skeletal Muscle. Scientific reports. 2017;7:42296. [PubMed: 28176881]
95. Miller PG, Shuler ML. Design and demonstration of a pumpless 14 compartment microphysiological system. Biotechnology and bioengineering. 2016;113(10):2213–2227. [PubMed: 27070809]
96. Edington CD, Chen WLK, Geishecker E, et al. Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies. Scientific reports. 2018;8(1):4530. [PubMed: 29540740]
97. Wagner I, Materne EM, Brincker S, et al. A dynamic multi-organ-chip for long-term cultivation and substance testing proven by 3D human liver and skin tissue co-culture. Lab on a chip. 2013;13(18):3538–3547. [PubMed: 23648632]

98. Wang G, McCain ML, Yang L, et al. Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies. Nat Med. 2014;20(6):616–623. [PubMed: 24813252]

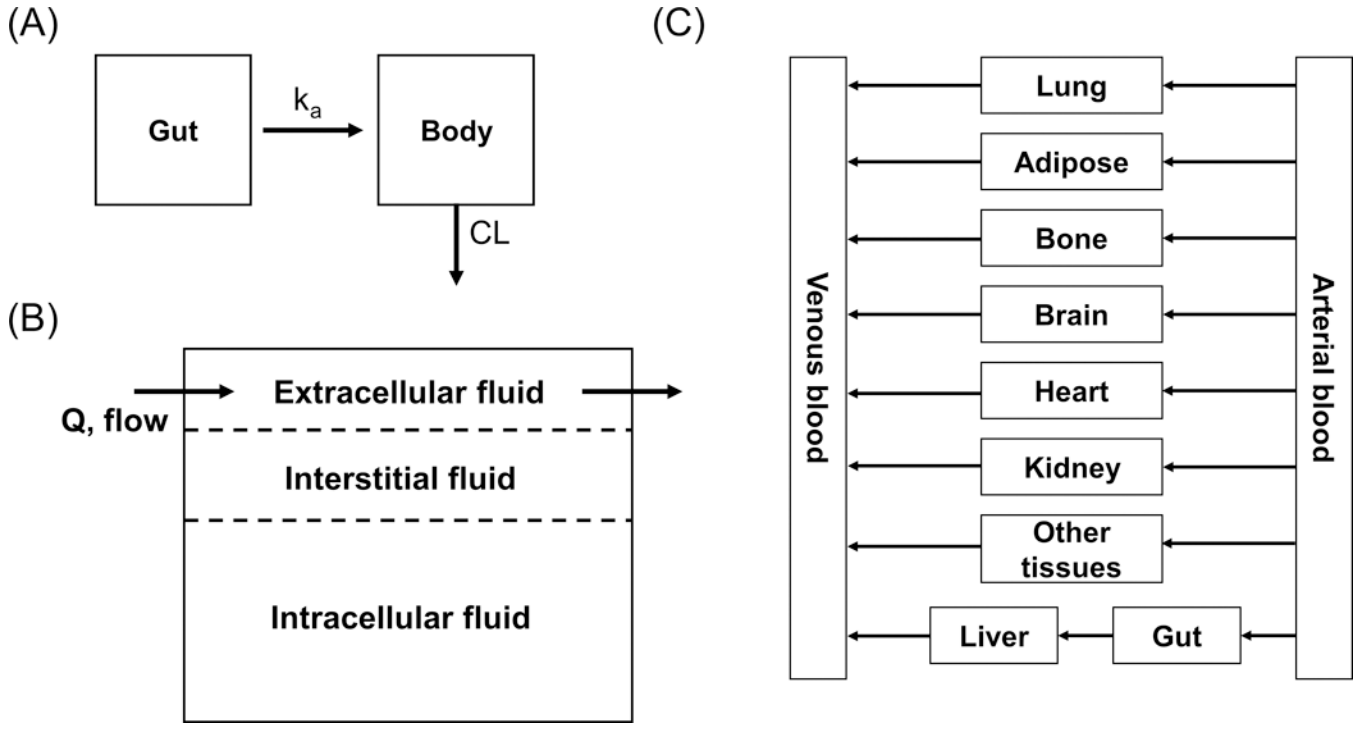

Figure 1.
Various forms of PK models. (A) Two compartment model; (B) Compartment model with segmentation; and (C) PBPK model.

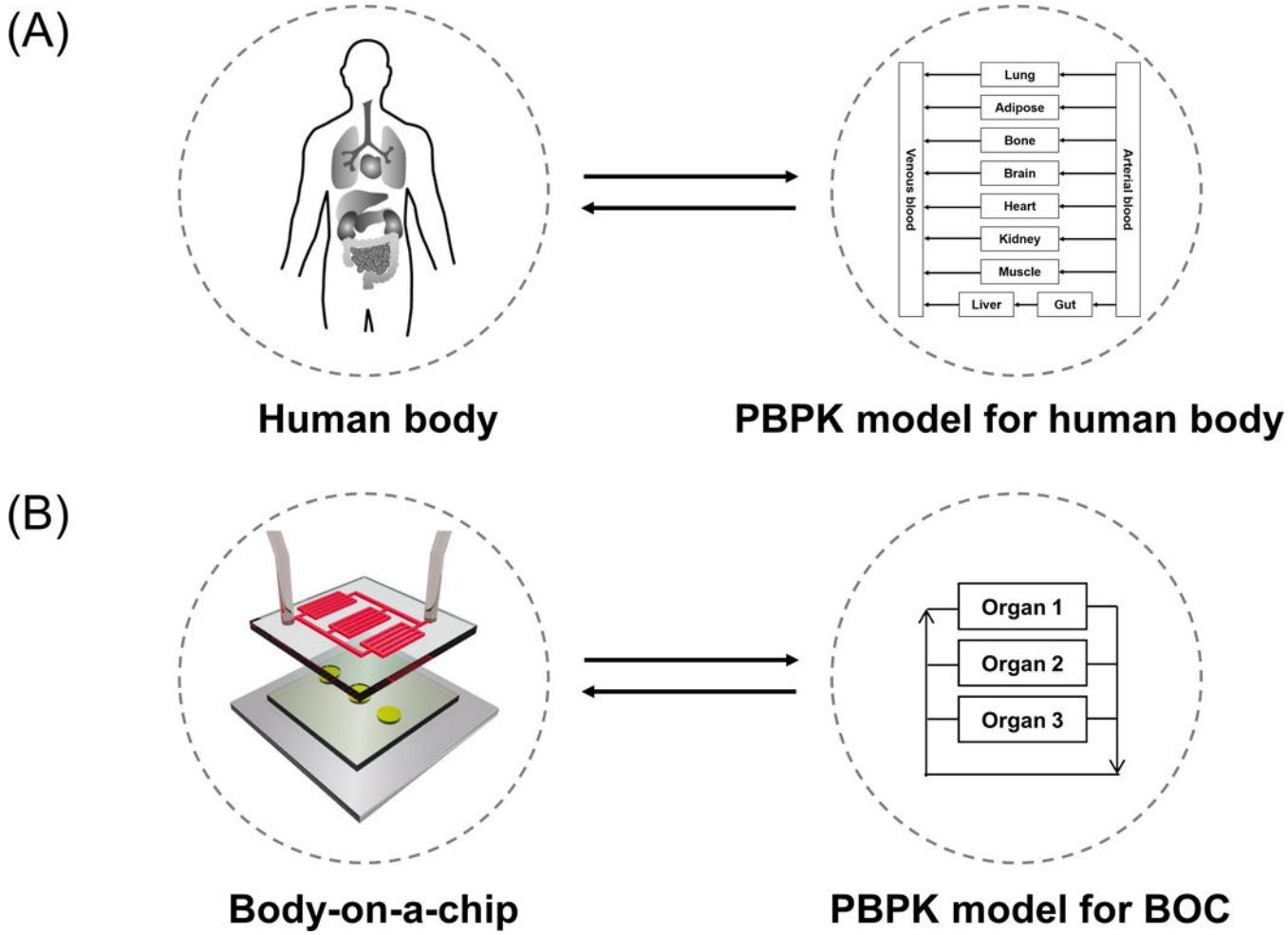

Figure 2.

(A) Schematics of the human body and its corresponding PBPK model. (B) Representative body-on-a-chip system and its corresponding PBPK model. The BOC model can be made more complex, for example, BOC system with 14 organ compartments.82