Scaling and systems biology for integrating multiple organs-on-a-chip

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***Short Abstract* — Coupled systems of *in vitro* microfabricated organs-on-a-chip containing small populations of human cells are being developed to address the formidable pharmacological and physiological gaps between monolayer cell cultures, animal models, and humans. These gaps present challenges not only in tissue and microfluidic engineering, but also in systems biology: how does one model, test, and learn about the communication and control of biological systems at the scale of individual organs on chips? Allometric scaling provides some guidance, but appropriate biochemical and functional scaling of multiple organs and a universal cell-culture medium are critical to proper systems function and valid pharmacological interpretation.**

***Keywords* — Organs-on-Chip, human organ constructs, scaling laws, pharmacokinetics/pharmacodynamics (PK/PD), systems biology, interorgan signaling, microbioreactors.**

I. Purpose

Organ-on-a-chip (OoC) technologies have advanced considerably in the past decade[1,2]; however, understanding of biological scaling laws and how they apply to multiple, coupled OoCs has been largely ignored. To replicate human physiology and drug response with interconnected human organs-on-a-chip (OoCs) and larger human organ constructs (HoCs), it is critical that each OoC/HoC has the correct relative size. Extensive literature describes differences in organ size between animal species whose body mass, *M,* spans 6 orders of magnitude. Organ size does not scale proportionally (isometrically) with *M*, but instead obeys a number of different allometric power laws that describe, for example, how as the animal's linear dimension L increases, its mass increases as L^3, and hence the cross-sectional area of the bones must increase out of linear proportion [3]. Metabolic rates scale as $M^{3/4}$, blood circulation time scales as $M^{1/4}$, and pulmonary and vascular networks exhibit $M^{3/4}$ scaling [4].

A variety of scaling criteria may be adopted for coupled OoCs/HoCs. An example OoC system represents 10^{-7} of the alveolar surface of a human lung, *i.e.,* 0.1 microlung [5], and an HoC bioreactor creates 10^{-3} of a human liver, *i.e.,* 1 milliliver [6]. When multiple organs are connected, their relative size could be normalized to mass, surface area, volumetric flow, or other geometric measures. Allometric laws could be used to construct human organs sized to a mouse, albeit with very high heart rates and pharmacokinetics and pharmacodynamics (PK/PD) that might represent a mouse better than an adult human. Given that cells in OoCs/HoCs may not operate with the same efficiency as cells *in vivo*, it may be more realistic to construct an OoC/HoC system that reflects a small fraction of an adult human, *i.e.,* that represents, in effect, living histological "sections" of an adult human.

II. Issues to Consider in Building a MilliHuman

As organs are made smaller, scaling must ultimately fail, since individual cells have a fixed size, and immune cells, for example, function in isolation and at low densities. The circulating volume of perfusate of an OoC/HoC system must match organ size, lest metabolites, hormones, and paracrine signals be diluted to the point that each organ operates in a large reservoir independent of the other organs. A universal media may be needed to maintain multiple cell types. Cellular heterogeneity, critical to cellular signaling pathways *in vivo*, can be hard to maintain for long times *in vitro*. Coupled non-linear biological systems can spontaneously oscillate and may require external stabilization. Signaling molecules from missing organs must be provided. It would be useful to apply localized biochemical perturbations to assess the response of the other organs. It is important to realize that OoC/HoC systems reside in a niche of abstraction that will improve constantly with technology but will never exactly recreate a full human. It may be most useful if OoCs and HoCs are viewed as simplified model systems for PK/PD and systems biology studies, not small humans.

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