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A generative modeling approach to connectivity—Electrical conduction in vascular networks

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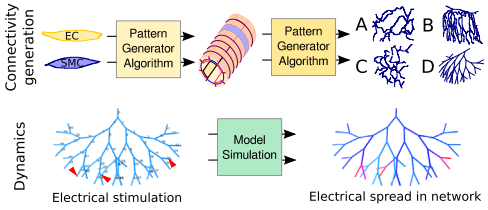
HIGHLIGHTS

- Strategy for dynamical models: Generate connectivity using pattern-algorithms.
- Software generates electrical models of arbitrary vascular networks from cell level.
- Series of electrical conduction models generated in various vascular networks.
- Vascular morphology and connectivity delimit conduction capacity within networks.

GRAPHICAL ABSTRACT



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ABSTRACT

The physiology of biological structures is inherently dynamic and emerges from the interaction and assembly of large collections of small entities. The extent of coupled entities complicates modeling and increases computational load. Here, microvascular networks are used to present a novel generative approach to connectivity based on the observation that biological organization is hierarchical and composed of a limited set of building blocks, i.e. a vascular network consists of blood vessels which in turn are composed by one or more cell types. Fast electrical communication is crucial to synchronize vessel tone across the vast distances within a network. We hypothesize that electrical conduction capacity is delimited by the size of vascular structures and connectivity of the network. Generation and simulation of series of dynamical models of electrical spread within vascular networks of different size and composition showed that (1) Conduction is enhanced in models harboring long and thin endothelial cells that couple preferentially along the longitudinal axis. (2) Conduction across a branch point depends on endothelial connectivity between branches. (3) Low connectivity sub-networks are more sensitive to electrical perturbations. In summary, the capacity for electrical signaling in microvascular networks is strongly shaped by the morphology and connectivity of vascular (particularly endothelial) cells. While the presented software can be used by itself or as a starting point for more sophisticated models of vascular dynamics, the generative approach can be applied to other biological systems, e.g. nervous tissue, the lymphatics, or the biliary system.

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1. Introduction

The integrative behavior of a biological system depends on the dynamic interactions among its constituent parts. Whereas reductionism advocates study of constituent parts, biological

Abbreviation: EC, endothelial cell; GJ, gap junction; MEGJ, myoendothelial gap junction; ODEs, ordinary differential equations; SMC, smooth muscle cell; V_m, membrane potential; $V_{m,rest}$, resting membrane potential

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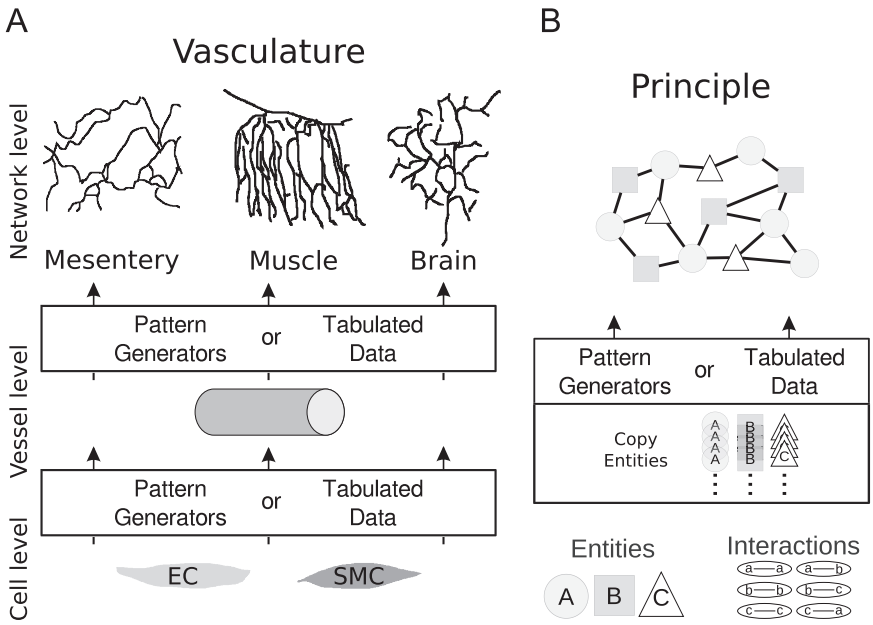

Fig. 1. Basis of generative modeling approach to connectivity. (A) Vascular beds differ structurally. Structural differences are obvious from network topology but can also exist at both vessel and cell levels. The basic idea is that larger structures are generated from smaller structures via "pattern generators" or "tabulated data" (see text). Usually, tabulated data is more frequent at macroscopic levels and pattern generation occurs at microscopic levels. (B) The "lego block principle" uses object-oriented programming to describe each entity (only low level entities are depicted) of the biological system as a *type* that can hold a unique index and entity specific parameters. Sets of ODEs describing (1) internal dynamics of each entity, and (2) interactions among the entities are collected. Using a pattern generator algorithm and/or tabulated data, the calculated number of entity-objects can be copied from each entity-type and the relevant sets of connectivity produced, one set for each type of interactions. Objects can be arbitrarily organized but connectivity generation must be based on biological observations.

function usually arises from multicellular interactions. Indeed, many biological systems display salient structural features that influence global behavior, e.g. the network structure of different vascular beds (Cassot et al., 2006; Hirsch, 2012; Segal, 2005), see Fig. 1A. The isolated impact of structure can be studied using mathematical modeling. Modeling of structural changes in spatially extensive systems, however, is laborious as changes in connectivity necessitate model reorganization. Here, a general strategy to ease connectivity generation across multiple spatial scales in dynamical models is presented using electrical signaling in the vascular wall as an example.

Microvascular networks represent highly dynamical and extensive spatial systems that rapidly redistribute blood flow to underperfused areas within a tissue (Hill, 2012; Segal, 2005). Networks display distinct structural differences between vascular beds, e.g. skeletal and cerebral circulations (Segal, 2005; Cassot et al., 2006), yet the structural impact on vascular tone regulation is relatively unknown (Hirsch, 2012). Conversely, constituent endothelial cells (ECs) (Nilius and Droogmans, 2001; Mehta and Malik, 2006) and smooth muscle cells (SMCs) (Longden et al., 2016; Yamamoto et al., 2001; Cole and Welsh, 2011; Hill et al., 2006) are well-studied as they underlie a host of regulatory mechanisms controlling local vascular tone (Segal, 2005; Somlyo et al., 1999; Hill et al., 2006). Electrical communication between vascular cells is critical to integration of the local vasomotor responses across a network (Tran et al., 2012; Hill, 2012; Segal, 2005). A local electrical signal rapidly disperses via gap junctions (GJs) between vascular cells. Electromechanical coupling in SMCs converts the signal into a conducted vasomotor response that coordinates tone across long distances within the network (Emerson et al., 2002; Tran et al., 2012; Xia and Duling, 1995; Segal et al., 1989). Theoretical studies have shown that not only electrical properties of ECs and SMCs but also cell orientation and number of SMC layers (i.e. capacitive load) influence conduction (Diep et al., 2005; Kapela et al., 2010; Hald et al., 2015). We therefore hypothesize that connectivity and morphology of vascular structures in general delimit electrical communication within a vascular network. Consequently, the aims of the present paper were threefold: (a) To present a novel strategy to generate connectivity in computational models of dynamical systems. (b) To apply the strategy in an open source software that generates dynamical models of arbitrary vascular networks from cell level to the network level (in the following, the software is called 'the vascular model generator'). Each level may be furnished with particular dynamics and/or connectivity. (c) To use the vascular model generator to study the impact of network structure and topology on electrical spread (see below).

Existing software platforms mostly focus on dynamics and changes herein, notably biochemical reaction-networks, intracellular cell-signaling or regulatory systems (see http://www.systems-biology.org/software/simulation/). Except from large projects such as 'TheVirtualHeart.org', few platforms handle spatial changes (Stoma et al., 2011; Cornelis et al., 2012) and none addresses spatially extensive systems. Here, a "lego block principle" is used to model the basic entities of a system (the EC, the SMC, and the vessel) and their interactions. Subsequently, connectivity between entities is generated from either algorithms that approximate the organization of entities or from tabulated morphometric data. The presented vascular model generator can therefore be used in conjunction with recent methods for detailed 3D reconstructions of vascular network topology based on integrative 3D imaging from disparate sources (Rieger and Welter, 2015; Kim et al., 2012; Blinder et al., 2013; Hirsch, 2012), ex vivo vascular castings (Cassot et al., 2006; Hirsch, 2012), or synthetic reconstructions (Schneider et al., 2014). Such reconstructions are commonly used to analyze network topology (Blinder et al., 2013; Cassot et al., 2006; Hirsch, 2012) or to model e.g. hemodynamics (Kim et al., 2012; Rieger and Welter, 2015; Reichold et al., 2009) or vascular remodeling (Pries and Secomb, 2014; Jacobsen et al., 2003). Due to the separation of dynamics and connectivity, the vascular model generator can also be applied to model dynamics of other phenomena in vascular networks, e.g. nephron synchronization or vascular remodeling

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