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Unraveling liver complexity from molecular to organ level: Challenges and perspectives

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ABSTRACT

Biological responses are determined by information processing at multiple and highly interconnected scales. Within a tissue the individual cells respond to extracellular stimuli by regulating intracellular signaling pathways that in turn determine cell fate decisions and influence the behavior of neighboring cells. As a consequence the cellular responses critically impact tissue composition and architecture. Understanding the regulation of these mechanisms at different scales is key to unravel the emergent properties of biological systems. In this perspective, a multidisciplinary approach combining experimental data with mathematical modeling is introduced. We report the approach applied within the Virtual Liver Network to analyze processes that regulate liver functions from single cell responses to the organ level using a number of examples. By facilitating interdisciplinary collaborations, the Virtual Liver Network studies liver regeneration and inflammatory processes as well as liver metabolic functions at multiple scales, and thus provides a suitable example to identify challenges and point out potential future application of multi-scale systems biology.

1. Introduction

The complexity of biological systems is determined by multiple factors. Among them the interplay of regulatory mechanisms at different scales is central. In the last decades the application of omics techniques aimed at collecting comprehensive information on biological systems has led to the generation of a vast amount of data from gene to protein level, and is currently being extended towards the whole cell, the tissue, and whole body level. The analysis of the collected data has required the development of new bioinformatic tools and mathematical modeling approaches, and it has become evident that an understanding of biological systems requires a multidisciplinary approach addressing multiple scales (Beard et al., 2012; Cristini, 2010; Noble, 2002; Schnell et al., 2007; Southern et al., 2008; Viceconti, 2012).

Such approaches integrate the knowledge acquired from different fields such as physics, biology, mathematics and bioinformatics, and increasingly the need to share experimental data as well as computational methods is realized (Bradley et. al., 2011; Britten et al., 2013; de Bono et. al., 2013; de Bono and Hunter, 2012; Shi et al., 2013; Wittig et al., 2012).

Classically, models addressing several scales are known as multi-scale models. Multi-scale modeling in physics and engineering is known as a stratification of techniques in which models at coarser scales have in the best case been derived by rigorous methods such as hydrodynamic limits and homogenization from models on smaller scales (Deville, 2012; Presutti, 2009; Spohn, 1991; Tadmor, 2011). Often this link has also been made computationally, e.g. if parameters are calculated with a microscopic simulation and then fed to a model addressing a larger scale (Tadmor, 2011). The methods have been refined and expanded over

Abbreviations: VLN, Virtual Liver Network; SOP, standard operating procedure; HGF, hepatocyte growth factor; PI3K, phosphatidylinositol 3 kinase; ODE, ordinary differential equation; IL1, interleukin 1; IL6, interleukin 6; NFkB, nuclear factor κ-light-chain-enhancer of activated B cells; BMP6, bone morphogenetic protein 6; CT, computed tomography; MRI, magnetic resonance imaging; CCl_4, carbon tetrachloride; APAP, acetaminophen.

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decades from gases, fluids to solids, in the meantime addressing soft matter (Doi, 2013). For selected problems and scales similar approaches have been explored for multi-cellular systems as well (de Masi et al., 2007; Stevens, 2000), or can at least be constructed within certain limits (Alber et al., 2006, 2007; Drasdo, 2005). Discussing the different approaches in detail is beyond the scope of this paper, but the general trend is to consider continuum equations mimicking quantities for which conservation laws can be formulated as local densities (e.g. mass, momentum, angular momentum, energy, entropy) at spatial scales much larger than the individual units. At scales of a few individual units or in case of inhomogeneities between neighboring units, the individual units shall be modelled as agents (Preziosi and Tosin, 2009; Qu et al., 2011). Intermediate, hybrid-type, models where high resolution models of individuals are coupled to low resolution models of the same individuals may be important future options permitting zooming locally in and out as successfully demonstrated for biomolecules (Ayton et al., 2007).

However, the challenges faced in living systems are often quite different and reach far beyond the classical picture of multi-scale analysis. In living systems the processes at different scales are largely interacting, and, if processes at cell, tissue or organ scale are considered, the number of potentially involved components and processes at lower scales can be huge (Kitano, 2002; Noble, 2002; Schnell et al., 2007). Accordingly, the term "multi-scale" in multi-scale modeling of tissues is often used in the sense of integrating the functional units of interest into one model that spans the different levels involved in the processes of interest, hence addressing multiple levels (Southern et al., 2008; Wolkenhauer et al., 2014).

The impact of one scale on another is not unidirectional e.g. from small to large scales as from genes and proteins to cells, but bi-directional as, for example, interactions between cells can feed back to gene expression and protein interactions, whereby the quality of feedback will generally depend on the cells' environment (Noble, 2012). A separation may be made between different functional units, that may each span different scales. A successful physiological analysis ultimately requires identifying and representing all important system components, and their interactions in a model (Noble, 2002). It remains to be discussed if this should lead to performing a virtual "copy" of nature (Noble, 2002) or representing the important functionalities of each component in a reduced model. The best way to approach problems of that complexity is still being debated (Majumder and Mukherjee, 2011; Southern et al., 2008) but there is a tendency in the community to start from the level at which the richest data exist, which usually corresponds to a "middle-out" as opposed to "top–down" or "bottom–up" approach (Noble, 2002).

Technically, linking the levels may either be achieved by linking different codes each addressing a single level (at risk that two interacting codes each require different accuracies, and out of their coupling effects may emerge that are difficult to predict), or generating rather one big model spanning all scales and incorporating their levels into the same code at risk of an overflow of coding complexity (Bradley et al., 2011; Southern et al., 2008). As rigorous coarse graining at this degree of complexity is either hard to achieve, not possible, or not adequate, model reduction, simplification or abstraction remain largely a matter of intuition.

A major challenge when composing multi-scale models is to find a language in which to express the model itself as well as its interfaces to other models and users. So far multi-scale models are typically built by combining multiple mathematical and physical sub-models expressed in terms of mathematical equations, algorithmic concepts and components expressed as pseudo or source code and experimental or other input data in often proprietary software frameworks. However, in order to ensure reproducibility and allow for communication, exchange and collective development of multi-scale models, a model description language able to precisely describe each of these components is needed (de Bono and Hunter, 2012). While for certain sub-classes of models comprehensive and well-formulated description languages already exist, for example SBML and CellML for Boolean and ordinary differential equation (ODE) models, a similar language for multi-scale models still remains elusive.

The virtual heart as pioneer in the field of multi-level physiological modeling is based upon the successful work of Hodgkin and Huxley (Hodgkin and Huxley, 1952), and extended over several decades to include electrophysiology, flow and mechanics, linked to the genetic, molecular, cell, tissue and organ level (Hunter et al., 2003; Noble, 2002). These activities facilitated patient-specific simulations (Chapelle et al., 2013; Delingette, 2007; Sermesant et al., 2009) that have given valuable insight from which other interdisciplinary initiatives that address other organs or complex diseases using in-silico approaches can learn. In large parts of the scientific community, the multi-scale/multi-level approach now becomes increasingly accepted, leading to huge efforts in various fields. A prominent example is multi-scale cancer modeling and in-silico oncology (Cristini, 2010; Deisboeck et al., 2011). For multi-scale modeling of tumors often agent-based models have been considered, as those facilitate direct representations first of molecular components inside the cell, and second of detachment of cells from the main tumor mass as it occurs during invasion, intravasation and extravasation (Martins et al., 2007; Ramis-Conde et al., 2009, 2008). May et al. (2011) and Ribba et al. (2006) address cancer therapy models using cellular automaton models on a lattice as component to model individual cells. However, as models increasingly aim at including realistic descriptions of the biomechanics, there is a recent trend towards using either lattice-free ("off-lattice") models in which each cells' position with time is calculated from an "equation of motion", summarizing all forces on that cell and its own micro-motility (Drasdo et al., 2007; Ramis-Conde et al., 2009, 2008; van Leeuwen et al., 2007), or models permitting for variable cell shapes to mimic deformation and compression of cells, either on a lattice (usually here the "Cellular Potts model is used") (Glazier and Graner, 1993; Jiang et al., 2005), or free from any lattice (Newman, 2005, Odenthal et. al., 2013).

An inevitable question is that of the most efficient organizational approach to push multi-scale/multi-level modeling forward. Small local initiatives integrating groups locally hence promoting direct communication, but with the threat that their background is too divergent, and their expertise not covering the requirements of the field? Individual small scale initiatives may take a long time to reach the maturity of virtual heart modeling. Or – at the other extreme – global network projects of partners that partially know each other and, at least on paper, cover all expertise necessary at the expense of difficult orchestration due to physical distance? Do today internet technologies help to bridge physical distance? Recently multiple network-based projects have been developed to face the complexity of modeling organ or animal physiology as a whole and achieve within years for what the virtual heart has taken decades (Hunter et al., 2013; Thiele et al., 2013; www.virtual-liver.de). Within the network-based projects focused on the liver, the Virtual Liver Network (VLN) aims to understand the complexity of liver function at all scales by combining experimental data with mathematical modeling (Fig. 1). As liver is the main detoxifying organ, besides gaining a better understanding of how information is generated and modified at different scales, or passes through different scales, there is also hope that modeling may promote development and evaluation of drugs and chemicals (Eissing et al., 2011; Niklas et al., 2013; Swat et al., 2011).