of simulated cells inside the lumen also conferred notable similarities to glandular carcinoma. On the other hand, dysregulation of the in silico principle governing proliferation had muted effects on growth morphologies. Comparatively, the 2 alterations and their misbalance gave rise to distinct morphologies that mark intermediate stages of a simulated progression toward malignancy. In cases where unchecked growth was observed, we identified structural patterns that are similar to observations of epithelial cancer in vivo, such as solid nests and regions of matrix surrounded by cells but in a disorganized pattern.

Conclusions: Considered together, our simulations demonstrate how computational models of this type can be interrogated and manipulated to test hypotheses and attain mechanistic insight that encompass seemingly varied aspects of morphogenesis in vitro. The results reaffirm the hypothesis that the composition and arrangement of the extracellular environment have a strong influence on overall morphogenic outcome. They also show that even a slight alteration or dysregulation of a normal in silico operating principle can cause substantial changes in growth characteristics, and suggest that the normal morphogenesis of epithelia tolerates very little deviation from strict adherence to principles of operation. Experimenting with simulation models of this type is expected to provide a potentially fruitful new strategy to gain deeper insight into the operational causes of oncogenesis and identify new targets of cell-based therapies for cancers of epithelial origin.

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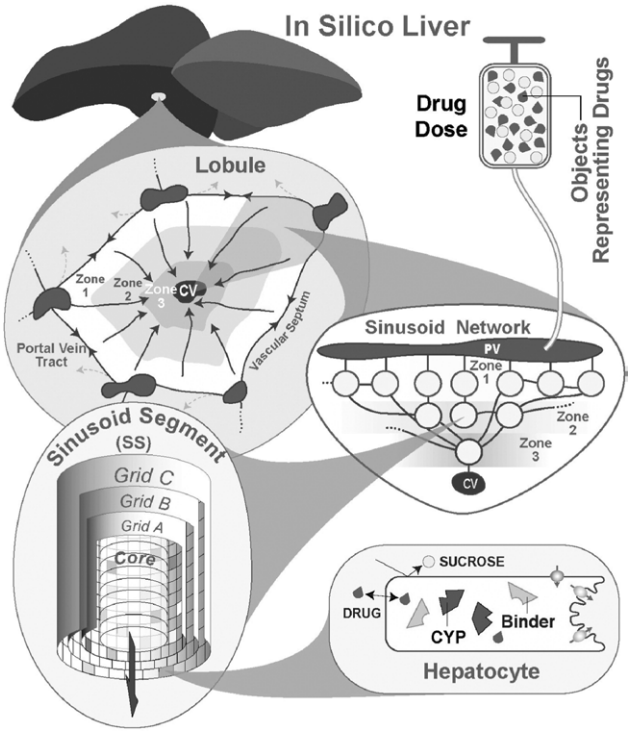

Fig. 1 Multiscale elements of liver architecture and physiology implemented in software.

The multiscale in silico liver

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Objectives: Validate a synthetic, physiologically based, mechanistic, multilevel, multiscale, In Silico Liver (ISL) for refining, exploring, and testing hypotheses about the mechanistic details of the hepatic disposition of antipyrine, atenolol, labetalol, diltiazem, and sucrose, administered alone or in combination, in normal and diseased organs. Enable the validated ISL to predict the disposition of prazosin and propranolol given only their physicochemical properties (PCPs).

Methods: Autonomous software objects representing hepatic components (metabolic enzymes, cells, microarchitectural details, etc) were plugged together to form a functioning liver analogue (Fig. 1). Structural features were represented separately from drug metabolizing functions. Each component interacts uniquely with mobile objects representing administered compounds. A single ISL structure was selected, parameterized, and held constant for all compounds. Simulated liver perfusion outflow profiles were recorded and compared with wet-laboratory data. Parameters sensitive to drug-specific PCPs were tuned so that ISL outflow profiles matched in situ profiles. To achieve the objectives ISLs needed to exhibit ten capabilities. (1) Accurately represents targeted intrahepatic events. (2) Establish clear physiologic mappings between liver and ISL components. (3) In silico data (in a type of Turing test) are indistinguishable from wet-laboratory data. (4) An ISL must be transparent so that simulation details are visualizable and measurable. (5) It must be easy to reconfigure an ISL to represent different hepatic or experimental conditions. (6) It must be relatively simple to change usage and assumptions, or increase or decrease detail, without requiring significant reengineering. (7) To facilitate capabilities 5 and 6, it must be easy to join, disconnect, replace, and separately validate ISL components. (8) ISLs must be usable for simulating the disposition properties of a variety of compounds, separately or in the same experiment. (9) A validated ISL must have methods available to predict PCP-sensitive parameter values of a new compound, given only its PCPs. (10) To enable and support these capabilities, ISLs ust use discrete interactions. Quantitative PCP-to-ISL mappings were implemented using 3 different parameter prediction methods: linear regression, a fuzzy c-means clustering algorithm, and a simple artificial neural network.

Results: We simulated the hepatic disposition and metabolism of atenolol, antipyrine, labetalol, and diltiazem, along with the coadministered sucrose. Simulation results were nondeterministic. In silico results that were indistinguishable from those measured during in situ experiments. We An iterative ISL refinement procedure led to a single, core PCP-insensitive ISL structure parameterization that could be used for all five compounds. Only the parameter values of PCP-sensitive, ISL components that interact differently with different compounds needed tuning. Monte Carlo variants of the resulting ISLs were used to simulate outflow profiles for all five compounds, alone or in combination. The consequences of changing PCP-sensitive, probabilistic parameter values were explored to better understand how a change in PCPs can be expected to alter ISL behavior. The ten PCP-sensitive, ISL parameter values for prazosin and propranolol were predicted from nine PCPs using each of the 3 quantitative mapping methods. Those values were then combined with the already-validated, drug-insensitive parameter values. Simulation of the resulting ISLs gave expected hepatic disposition details and outflow profiles for the 2 drugs.

Conclusions: A synthetic, agent-oriented ISL has been developed and successfully validated, enabling us to posit that static and dynamic ISL mechanistic details, although abstract, map realistically to hepatic mechanistic details in PBPK simulations. Predicted profiles (using each of the 3 sets of predicted parameter values) were surprisingly good matches to the observed profiles, strengthening the ongoing validation of ISL mechanisms. The results represent an important advance toward the efficient use of limited drug-specific data to make reasonably accurate predictions as to the pharmacokinetics of specific compounds, within and between species, as well as under a variety of patient-specific clinical conditions.

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Toward differential diagnosis of critical illness using mechanistic mathematical models: First application to clinical data

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Objectives: Quantitative tools for medical decision support may help to overcome our current inability to fully exploit the quantitative data acquired in the intensive care unit (ICU) for patient evaluation and therapeutic decision making. We have recently uncovered a novel link between the clinical concept of differential diagnoses and the structure of the Bayesian posterior probability distributions of parameters of a mechanistic model of cardiovascular physiology conditioned on observations (Zenker et al, PloS Computational Biology, 2007, in press). The objective of this study is to take the first steps toward validating this approach for practical application by applying the proposed methodology to real data.
Methods: Using a physiologic database of ~24 000 ICU patients admitted between 2001 and 2004 at the University of Pittsburgh Medical center, we identified 7396 intravenous fluid applications (IFA) of 500 mL over 1 hour where pre- and post-IFA measurements of arterial pressure, central venous pressure, and heart rate were available. We obtained a sample based representation of the 19-dimensional population distribution of parameters/initial conditions of the previously reported mathematical model of the cardiovascular system using the Metropolis-Hastings Markov Chain Monte Carlo algorithm (MH). The unnormalized likelihood was defined by evaluating a bandwidth adaptive kernel density estimate of the 6-dimensional population distribution of observations at the point in observation space to which the model maps the respective parameter/state vector. We identified 3 convenience, diagnostically distinct, subsets of 20 patients with increase in blood pressure after IFA Diagnoses of congestive heart failure (CHF), hypovolemic shock (HS), or vasodilatory shock (VS), were identified by discharge ICD-9 diagnostic codes. The posterior distribution of the 19 free parameters/initial conditions conditional on the pre- and post-resuscitation mean arterial blood pressure, central venous pressure, and heart rate was approximated for each individual patient using MH. With the exception of total intravascular volume, for which an informative prior distribution was computed based on body surface area, uniform priors supported on 1/3 to 3 times reported literature values were used. 2 million samples were drawn for each patient, of which the initial 25% were discarded, and, after 1:10 thinning, combined within each of the 3 groups. The resulting per-group posterior distributions of parameters were compared pairwise using the Kolmogorov-Smirnov test with a significance level of 5%. The median was used to approximately characterize differences in location.
Results: Visual comparison of 1- and 2-dimensional marginal distributions of observables resulting from population level inference indicated an accurate reproduction of the original data set. However, 1 and 2 dimensional marginal distributions on parameter/state space were found to be largely uninformative. In contrast, when comparing the grouped results of the inference performed on individual patients, we find that the groups differ in a statistically significant fashion in maximal unstressed venous volume (UVV), the midpoint of the myocardial contractility range (MC), and hydration index (HI, ratio of total intravascular volume to total unstressed volume of the large vessels), with CHF < VS < HS for UVV, CHF < VS < HS for MC, and HS < VS < CHF for HI. Although differences between distributions of systolic ventricular filling times attained statistical significance only for comparison of VS and HS (P = .06 for CHF vs HS and CHF vs VS), the order of medians was HS < VS < CHF. Furthermore, median diastolic ventricular stiffness was highest in CHF, while distributional difference failed to reach statistical significance.
Conclusions: The inferred population level parameter distribution, based on a data set featuring 2 time points on each of 3 observables in each patient, proved to be uninformative. This result indicates that, to identify structure in the population using this approach, a) richer observation data may be required, and b) priors on parameters that can be assumed to vary little or are known may need to be introduced. In contrast, with regard to individual inference, in spite of the minimal amount of data assimilated per patient, the observations were mapped to clinically meaningful distributions of directly interpretable physiologic parameters that, for key parameters, reflect the physiologically expected differences between the examined patient groups. This finding provides the first real-life validation of our fundamental approach. To obtain posterior distributions on individual patients that are sufficiently informative for useful diagnostic support, more data per patient will have to be assimilated, possibly in combination with stronger priors and more detailed models of the underlying physiology.

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Rule-based modeling of signal transduction

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Objectives: Our overall objective is to develop mechanistic models of signal transduction and other cellular regulatory processes that incorporate detailed knowledge about biomolecular