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***In Silico* Modeling of Respiratory Structure, Function, and Disease**

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The presence of both liquid and gas phases, combined with large changes in volume and shape during breathing create unique obstacles and challenges in our pursuit of a quantitative understanding of lung physiology. Mathematical models have historically played a critical role in the interpretation of complex experimental data sets, as well as generating new hypotheses which can subsequently be tested experimentally. Dramatic improvements in computational efficiency and speed, combined with advances in non-invasive imaging modalities over the past two decades have created exciting new opportunities to examine the pathophysiology of the lungs. This issue of *Drug Discovery Today: Disease Models* contains five reviews which address the role of *in silico* modeling of processes such as inhaled aerosol deposition, exchange of endogenous (nitric oxide) gases, parenchymal mechanics, and airway wall mechanics to ultimately enhance our understanding of lung function in both health and disease.

The use of *in silico* modeling to predict or capture “emergent phenomena” is an important theme of the reviews. An emergent phenomenon is an observable feature of a system which cannot be predicted by the individual behavior of its elements. In other words, a system of interacting components, characterized by non-linear interactions, feedforward control, and/or feedback control, produces new and unpredictable (i.e., emergent) features (or phenotypes). For example, the reviews by Winkler, Fabry and Fredberg discuss *in silico* models which describe the dynamic force-length relationship of airway smooth muscle and the forces which impact airway caliber. Early microscopic models [E1] addressing this topic [E2] were unable to predict the behavior of the entire airway tree during bronchoconstriction, which is characterized by spatially heterogeneous ventilation. Only recently, a model, which integrated features of the earlier models of smooth muscle tension with the interdependence of the airway tree, was able to predict patchy ventilation during bronchoconstriction.

An additional example for an emergent phenomenon is described in the review by Suki and co-authors: In fibrotic lung diseases, the rate of decline in lung function suddenly changes. In their review, the authors discuss the percolation theory to explain that this phenomenon results from a sudden decrease in the bulk modulus of the lung tissue when emphysematous or fibrotic regions are suddenly fully connected spatially throughout the system. This finding is potentially of relevance to the human situation, where “depercolating” the system might be an interesting therapeutic approach to prevent the decline in lung function in patients suffering from fibrotic lung diseases.

Another emergent phenomenon is discussed in the review by Shelley and colleagues, which focuses on the pulmonary exchange properties of nitric oxide, an endogenously produced gas

thought to be a marker of inflammation. Interestingly, clinically similar patients can have markedly different nitric oxide levels in the exhaled breath^[E3]. The authors review the current *in silico* efforts to understand exhaled nitric oxide concentration, and suggest that future models will need to integrate non-linear chemical reaction theory at the cellular level along with spatial ventilation and inflammation heterogeneity in order to predict this emergent phenomenon.

Finally, the review by Annapragada and Mishchiy highlights the role of *in silico* models in customizing inhaled aerosol therapy, emphasizing the importance of sheer computational speed. In the era of “personalized” medicine, our ability to simulate features such as aerosol deposition patterns within the unique geometries of each person will parallel the rate at which we can develop a patient-specific therapeutic regimen. This approach^[E4] completely encompasses the concept of predicting emergent phenomena by considering each individual as a distinctly unique phenotype. In the case of aerosol deposition, highly non-linear fluid dynamics result in a unique deposition pattern for each person, and this unique pattern can be considered an emergent phenomenon.

In most cases, individual system components (e.g., airway smooth muscle) can only be studied experimentally in isolation; in other words, by applying the reductionist approach to understanding a system. However, in order to predict behaviors of the larger system, mathematical models must be developed which capture the complexity of the interacting components. This is, in essence, a description of the broader and rapidly growing field of systems biology. The role of *in silico* modeling will continue to increase as we strive to reach our ultimate goal of understanding whole organ pathophysiology.

With best wishes,

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Biography

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