The investigation of biological systems such as the lung can be thought of as proceeding through a series of stages. The first stage is observational, involving the cataloguing of structures, patterns, and behaviors that impinge on our everyday experience at the macroscopic level. This leads to the initial formulation of hypotheses about what might be underlying such behavior, and is most readily associated with diagnostic medicine. This stage also typifies what might be called classical physiology. The second stage of investigation involves dissecting a system into its components and studying each in isolation. This is the reductionist approach that has dominated most of biomedical science since its inception and which has perhaps achieved its most profound expression in the advances of molecular biology. However, while a complete understanding of a system clearly has to include knowledge about its constituents, the prevalence and successes of the reductionist approach have tended to make us forget that the job does not end there. Indeed, the most important features of macroscopic biological behavior, particularly its pathological derangements, are not fully explicable simply in terms of constituents operating at the microscopic level.

To gain a complete understanding of a biological system, it is necessary to proceed through a third stage of research, the integrative stage, where a system’s components are considered as an ensemble. In contrast to reductionism, which seeks to find out what is inside the “black box,” integrative science attempts to determine how the box actually works. Here, the interactions between a system’s components are at least as important as the individual components themselves. Of necessity, reductionism must precede integration. This may explain in part why we have been so preoccupied thus far with the former, but this is not the only reason. Also at play is the fact that integration is invariably much more complicated to figure out than reductionism. What makes it so complicated is the phenomenon of emergence, defined as behavior that arises at one level of scale and is most readily associated with diagnostic medicine. This is exemplified by research into the link between lung structure and function, the subject of the present Highlighted Topic series in which computational modeling plays a prominent role.

The series begins with three mini-reviews that examine how aspects of lung function arise from the structural arrangement of its components. Nowhere is this more clearly illustrated than in the tree structures of the pulmonary airways and vasculature, the complexities of which can be seen to arise from relatively simple rules as explained by Glenny in “Emergence of matched airway and vascular trees from fractal rules” (4). Despite their structural complexities, however, evolution has seen to it that the vascular and airway tree structures are matched to each other in a way that allows for gas exchange to proceed with remarkable efficiency. Suki and Bates then deal with how the complex rheological properties of lung tissue arise from the way in which its constituent fibers, cells, and fluids interact at the microscopic scale in “Lung tissue mechanics as an emergent phenomenon” (10). This is a prime example of macroscopic physiological behavior that bears no qualitative resemblance to the behaviors of the underlying contributors and can be seen as an inevitable consequence of the macroscopic mechanical function of the lung. Another example of this phenomenon at a somewhat lower level of length scale is provided by the mechanical behavior of airway smooth muscle. Here, even behavior at the level of a single cell can be seen as an emergent phenomenon arising from a set of coordinated active processes at the molecular level, as shown by Seow and Fredberg in “Emergence of airway smooth muscle functions related to structural malleability” (9).

The May issue of the series features three mini-reviews that illustrate the seminal role of computational modeling in our understanding of lung function. Tawhai and Bates (11) begin by examining how multi-scale modeling is used to capture the essential features of emergent behavior in “Multi-scale lung modeling.” Here, the equations of Newtonian physics are applied to anatomically accurate representations of spatial structure to shed light on the airway hyperresponsiveness of asthma and to predict how the normal pulmonary vasculature functions. This is followed by an examination of how the emergence of spatial organization across the lung can occur during bronchoconstriction in “Self-organized patterns of airway narrowing” by Winkler and Venegas (12). Of particular note, these authors show how computational modeling predicts the occurrence of a “tipping point” as bronchoconstriction proceeds, where lung function suddenly transitions to a state of

The involvement of hierarchical organization and multilevel feedback loops. It has thus only been in the past few decades, corresponding to the availability of digital computers, that scientists have been able to begin a quantitative investigation of emergent behavior in biological systems. This is exemplified by research into the link between lung structure and function, the subject of the present Highlighted Topic series in which computational modeling plays a prominent role.

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severe impairment, an asthma attack, as a result of nonlinear interactions between multiple airway segments. Kaczka, Lutchen, and Hantos then show, in “Emergent behavior of regional heterogeneity in the lung and its effects on respiratory impedance” (5), how anatomically based computational modeling serves as the central paradigm for developing an understanding of the link between lung structure and function, the latter measured in terms of mechanical impedance. This is illustrated with respect to the functional derangements characterizing asthma, chronic obstructive pulmonary disease, and acute lung injury, three disease of enormous societal importance.

Finally, in the June issue, Frey, Maksym, and Suki (3) introduce the role of time into the discussion of emergent behavior in the lung in “Temporal complexity in clinical manifestations of lung disease.” Here, they show how a careful analysis of apparently random fluctuations in a data time series can often lead to the discovery of underlying order that harbors important predictive power, in this case related to the likelihood of having an exacerbation of severe symptoms of lung disease. The series is then concluded with an overview of what emergent behavior means for pulmonary medicine in “Complex systems in pulmonary medicine: a systems biology approach to lung disease” by Kaminsky, Irvin, and Sterk (6). This puts the system approach to pulmonary physiology into the wider context of systems biology in general.

These mini-reviews cover some of the currently active areas of research into the thorny question of how the macroscopic function of the lung arises from the details of its structure over many different levels of length and time scale, and how such emergence influences pulmonary medicine. This is an area of research that is still relatively new, particularly in terms of the role played by computational modeling. Nevertheless, it is becoming apparent that the reductionist approach to science on its own has not delivered what had been predicted (7) and is not likely to solve many of the most important (and most difficult) problems in biology. To do this, integrative approaches are needed that will elucidate how the fruits of the reductionist approach can be combined in complex and unexpected ways to yield the biological structures, patterns, and behaviors that impact our daily lives. Indeed, the rapidly growing realization of this reality is itself a kind of emergent phenomenon, reflecting a tipping point in awareness within the scientific community that has been spawned by the successes of reductionism and the extraordinary recent growth in computer and information technologies. Here, surely, lies the future of physiological research.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**REFERENCES**