Methods: An agent-based model was created consisting of relevant cells and their behaviors. The model's parameters were chosen to match experimental data on *Escherichia coli* infection in rats. The model was modified incrementally to include a wider range of immune system responses, including a feed-forward loop of inflammation-damage-inflammation, along with fibroblasts and an explicit healing response.
Results: Reproducing experimental data, the simulation shows that as the number of bacteria increased, so did the amount of damage experienced by the virtual host. With the higher number of bacteria, the amount of damage is sustained over a longer period, and the healing process takes longer. With the addition of fibroblasts, the amount of damage is dramatically lowered. With a lower initial level of fibroblasts (10 initially), the damage reached more than 100 arbitrary units. With a much higher amount of the fibroblast (100 initially), the damage stayed below 20 arbitrary units.
Conclusions: As our simulation clearly demonstrates, introducing an explicit healing function represented by fibroblasts reduces the capacity of bacteria to cause tissue damage. The model is an effective tool in that it allows the user to easily create a number of "what if" scenarios by manipulating several variables at once, including the initial level of bacteria, the initial number of macrophages, and the projected life span of the inflammation and antiinflammation cells. Not only are the results tied to realistic data, but also the model allows for predicting future outcomes based on those known parameters. We are currently working on an interface to make this simulation accessible to students.

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An indirect response model of endotoxin-induced systemic inflammation

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Objectives: The complex and multiplex characteristics of the acute inflammatory response (AIR) and its complications have been thought to be a leading potential reason for the inability to propose effective clinical intervention strategies. The nature of the response has lead researchers to the realization that mathematical models of AIR might provide rational leads for the development of strategies that promote the resolution of the response and the eventual establishment of homeostasis. Combinations of in silico and in vivo approaches are emerging as viable analysis strategies. Ab initio development of predictive models of complex biologic processes, such as AIR, is not possible. Therefore, model development needs to be based on relevant experimental measurements with appropriate injury models. Most prominent among them are animal models aiming at modeling production levels of key inflammatory cytokines. However, isolated elements of the response may not best characterize complex underlying phenomenon. Therefore, in this study, we propose to address to 2 critical questions: (*a*) what constitutes an underlying dynamic response, and (*b*) what is the structure of an appropriate inflammation model.
Methods: Gene expression in whole blood leukocytes was determined immediately before and at 2, 4, 6, 9, and 24 hours after intravenous administration of bacterial endotoxin to healthy human subjects. (The data used were generated by the Inflammation and Host Response to Injury Large Scale Collaborative Project funded by the National Institutes of Health.) Parts of these data have been used in previously published reports (PNAS 2005;102:4801-4806; Nature 2005; 437:1032-1037; however, the analyses in this article represent an approach that has not been previously published). First, we identify a set of distinct and coherent transcriptional profiles that are maximally affected by the endotoxin stimulus, and therefore, they can be used to describe the dynamic progression of the perturbed biologic system. One of the key aspects of our approach is the efficient decomposition of the entire dynamics of the system into its critical components. We apply a symbolic representation of time series data that allows for clustering probe sets that are highly similar in gene expression profile. Based on the statistically significant expression motifs, we apply an optimization-based algorithm that reveals 3 distinct temporal responses that are maximally affected by the stimulus—henceforth termed *essential responses*. These 3 essential responses, along with a standard pharmacodynamic model for simulating the clearance of endotoxin, are combined in an integrative PK/PD model using the principles of indirect response. The resulting model is described by a set of coupled ordinary differential equations containing the key aspects of inflammation such as proinflammation, antiinflammation, and organ dysfunction. Such quantifiable models are critical enablers toward understanding the connectivity of the critical components of the immune system, the relationships among various components, and offers opportunities for unraveling the control mechanisms of the onset and resolution of systemic inflammation.
Results: One of the key aspects of our approach is the efficient decomposition of the entire dynamics of the system into its critical components. We identified 3 distinct temporal responses that are maximally affected by the stimulus and include the proinflammatory response, composed of proinflammatory mediators functionally associated with cytokine and chemokine activities; the antiinflammatory response, composed of antiinflammatory mediators such interleukin 10; and a final response characteristic of tissue damage leading to organ dysfunction, composed of genes associated with the bioenergetics of the system. The tissue damage response characterizes the deficiency in the bioenergetics of the system, and impaired bioenergetics can lead to organ dysfunction. Our PK/PD model aims at identifying the optimal values of a set of parameters that contribute to the best interconnectivity of the critical inflammatory components. The proinflammatory response is modeled as a first-order differential equation, which consists of 2 stimulatory functions that describe the positive feedback of both the inflammatory stimulus and the tissue damage response to its zero-order production rate, and also, it consists of one inhibitory function that models the negative feedback of the antiinflammatory mediators to its synthesis rate. The antiinflammatory response is stimulated both by the proinflammatory mediators and the tissue damage response, and it is eliminated by a first-order degradation rate. Finally, proinflammatory mediators stimulate the tissue damage response. Our model allows us to explore the complex nature of inflammation by simulating the essential dynamics of the system, which, in human endotoxemia, reflect an inflammatory response that completely resolves by approximately 24 hours. Moreover, modeling the critical inflammatory components, it can help us to predict conditions that account for situations in which the inflammatory response has not been resolved.

Conclusions: We have presented a framework for assessing the inherent dynamics of acute inflammatory response and have proposed a potential network of interacting components that may reveal critical events of the onset and resolution of the AIR. The main conclusion of this work is that large-scale genomic studies can, if properly analyzed, reveal the intrinsic dynamic of the AIR, the constitutive elements of which can be rationally integrated within the framework of an indirect response model to provide clues as to the nature of the interactions among the various components.

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Cardiopulmonary variability during staged incremental exercise using a novel continuous individualized multiorgan variability analysis system

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Objectives: We hypothesize that complex physiologic dynamics are dependent on the integrity of the system generating them. Therefore, our objectives are to (*a*) develop a novel system for continuous individualized multiorgan variability analysis (CIMVA) focused on cardiac and pulmonary rhythms, in an effort to track emergent properties over time of complex physiologic systems, and (*b*) test the CIMVA system by evaluating changes in cardiopulmonary variability (CPV) during controlled physiologic stress, namely, staged incremental exercise in healthy subjects.
Methods: The CIMVA system (developed in Windows Matlab) comprises algorithms for computing and visualizing mean, SD, location of nonstationarities, fast Fourier transform (FFT), sample entropy (SampEn), multiscale entropy (MSE), wavelet analysis, detrended fluctuation analysis (DFA), kurtosis, skewness, power law analysis, and time irreversibility statistics. To accomplish continuous variability analysis over time, we used a roving window approach, whereby a window of user specified width and step marches through the input signal, computing and time stamping the above variability metrics at each step, thus creating multiple variability time series. Interval-in-time variability (instantaneous) and change in variability over time (evolution) are displayed on 2 parallel monitors. CPV is computed and visualized by synchronizing cardiac and pulmonary variability data streams, followed by plotting their "time evolution" on an X-Y plane. To test the CIMVA system, we performed staged incremental exercise tests were performed on healthy volunteers (n = 8), during which continuous heart rate (Brytech, 500 Hz EKG System) and respiratory rate (Respironics, 200 Hz Capnograph System) data were harvested. For analysis, EKG waveforms were converted to RR′ time series using Hamilton-Tompkins QRS detection algorithm, whereas end-tidal CO_2 waveforms were converted to breath-to-breath time series using a novel breath detection algorithm.
Results: The CIMVA system demonstrated robustness in continuously analyzing, visualizing, and storing CPV associated with heart and respiratory rate data sets. A reproducible decrease in wavelet, DFA, and power law CPV was observed with exercise for all subjects, and this decrease was progressive and continuous (Fig. 1). Certain measures of CPV, namely, FFT, power law, SampEn, and MSE, demonstrated higher sensitivity to nonstationarity in the analyzed data, wherein the progressive decrease in CPV was less pronounced and not continuous. The remainder of the variability statistics computed by the CIMVA system conformed to existing hypotheses regarding characteristic changes in CPV due to mechanical loading or exercise.
Conclusions: We conclude that an automated analysis of continuous individualized multiorgan variability, using a plurality of variability analysis techniques simultaneously, is feasible, reproducible, and allows us to study the change in multiorgan

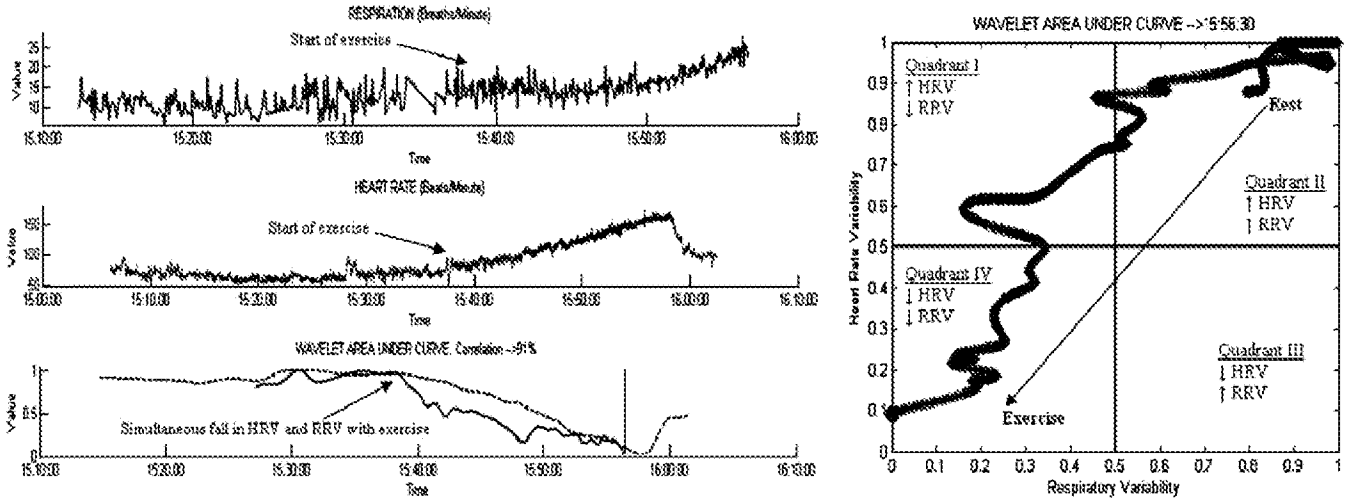

Fig. 1 Assessment of wavelet-based heart rate variability (HRV), respiratory variability (RRV), and cardiopulmonary variability (CPV) during a staged exercise test. The top panel on the left displays the respiratory rate (RR) in breaths per minute and the middle panel displays the heart rate (HR) in beats per minute—both measured simultaneously. The bottom panel on the left displays the normalized individual wavelet-based variabilities for the RR and HR signals—the solid plot displays RRV, whereas the dotted plot displays HRV. There exists a strong correlation of 91% between the wavelet-based HRV and RRV as depicted in this bottom panel—both variability curves tend to drop simultaneously after the initiation stage exercise testing. The normalized 4-quadrant plot on the right characterizes the evolution of CPV, which shows a progressive and continuous decrease from rest to exercise—from quadrant 2 (high HRV, high RRV) to quadrant 4 (low HRV, low RRV).