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

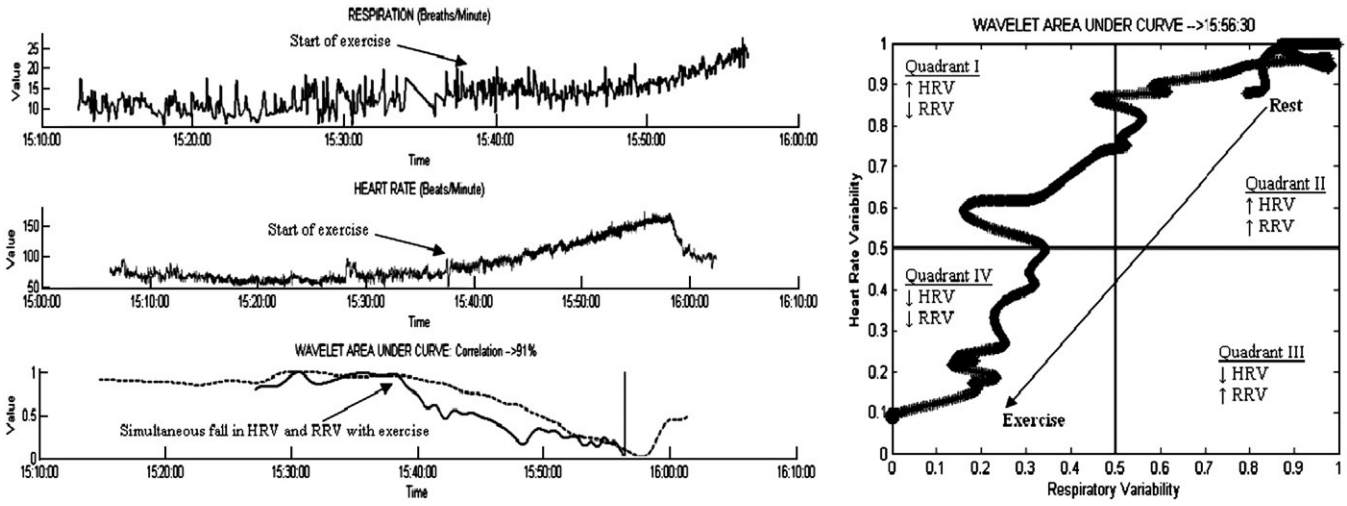

Fig. 1 Assessment of wavelet-based heart rate variability (HRV), respiratory variability (RRV), and cardiopulmonary variability (CPV) during a staged exercise test. The top panel on the left displays the respiratory rate (RR) in breaths per minute and the middle panel displays the heart rate (HR) in 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).

variability over time, a novel measure, in a comprehensive and accurate manner. A reduction in overall CPV associated with increasing levels of exercise is evident across the population studied. This software analysis has several clinical applications with promise toward the development of a real-time diagnostic and predictive multiorgan variability analysis system.

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Clinical and methodological impact of data set length reduction on measures of R-to-R interval complexity in prehospital trauma patients

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Objectives: The purpose of this study is to establish minimal data size suitable for remote assessment of status and noninvasive risk stratification using nonlinear analysis of ECG.
Methods: Ectopy-free 800-beat sections of ECG from 31 trauma patients during helicopter transport en route to a level I urban trauma center were identified from a database. Twenty patients survived (S) and 11 died (NonS) after arrival. Complexity of the R-to-R interval (RR) of the ECG was assessed via approximate entropy (ApEn) and sample entropy (SampEn), which quantify the randomness of the RRI; by fractal dimension by curve lengths (FDCL) and detrended fluctuation analysis (DFA), which assess the fractal scaling properties of the signal; and by similarity of distributions (SOD), which explores the probability of similar RRI amplitude distributions over time. Autonomic status was assessed by complex demodulation, which measures the amplitude of the low (LF_CDM) and high (HF_CDM) frequency modulations of the heart. Univariate analysis was used to screen variables, and logistic regression analysis (LRA) was then used to identify independent predictors of mortality. Identical analysis was performed for 200 beats, 1-minute-long and 10-second-long data sets selected within the original 800 beats. Data are presented as means ± SEM.
Results: Results are summarized in Table 1. In the 800-beat data, ApEn and SampEn were highly correlated (0.99). In the 800-beat set, LRA revealed SampEn as independent predictors of mortality (area under the receiver-operating characteristic curve, AUC = 0.90). In the 200-beat data, SampEn was also an independent predictor of mortality (AUC = 0.90) with the ROC curve not different ($P > .999$) from the 800-beat–derived data. SOD separated NonS from S in the 800-beat, and 60- and 10-second-long data sets. Descriptive and hemodynamic data were not different between groups.
Conclusions: Complexity analysis using SampEn can be used to identify nonsurviving trauma patients in 200-beat data sets and, using SOD, in 1-minute- and 10-second-long data sets.

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Ensemble models for human immune response to influenza A virus infection

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Objectives: Mathematical models are essential tools in disease modeling. In our study, we construct ensembles of models that vary in parameter values and are ranked according to their likelihood to capture existing data or clinically available observations. Probabilistic predictions allow one to quantify individual variability of the immune response to specific virus characteristics. The results obtained from an ensemble model are probabilistic predictions of the dynamics that accurately represents the variability of responses in individuals. Objectives: Our main objective is to construct an ensemble model of the dynamics of influenza infection, which makes probabilistic predictions on the course of disease, finds the likelihood of each model representing individual immune response, and makes probabilistic estimates of the effectiveness of therapeutic interventions such as antiviral drug therapy. We develop methods to find the posterior distribution that contains all the information on the parameter space. Our main goal is to quantify uncertainty in model predictions due to parameter heterogeneity.
Methods: Based on our published ordinary differential equation (ODE) model by Hancioglu et al (JTB, 2007), an ensemble

Table 1

Variable	800 beat		200 beat		60 sec		10 sec	
	NonS	S	NonS	S	NonS	S	NonS	S
RRI_MN	543.91 ± 47.37	626.30 ± 29.47	546.18 ± 47.98	626.35 ± 29.14	545.55 ± 48.34	627 ± 28.80	550.64 ± 50.93	634.45 ± 30.59
ApEn	0.87 ± 0.06**	1.09 ± 0.04	0.76 ± 0.05*	0.87 ± 0.02	0.66 ± 0.04	0.65 ± 0.03	–	–
SampEn	0.80 ± 0.08**	1.10 ± 0.05	0.83 ± 0.08**	1.2 ± 0.07	0.85 ± 0.11	1.07 ± 0.13	–	–
FDDA	1.08 ± 0.02*	1.13 ± 0.01	1.14 ± 0.03	1.17 ± 0.02	1.14 ± 0.02*	1.21 ± 0.03	–	–
SOD	0.28 ± 0.04*	0.19 ± 0.02	0.28 ± 0.04	0.19 ± 0.02	0.29 ± 0.04*	0.19 ± 0.02	0.33 ± 0.06*	0.18 ± 0.02
DFA	0.93 ± 0.14	1.26 ± 0.08	0.84 ± 0.13	1.01 ± 0.07	0.72 ± 0.11	0.88 ± 0.09	0.29 ± 0.17	0.44 ± 0.16
LF_CDM	9.09 ± 4.15*	13.1 ± 2.11	8.27 ± 3.66*	12.85 ± 2	8.00 ± 3.26*	12.55 ± 2.18	8.36 ± 3.74	12.45 ± 2.38
HF_CDM	3.27 ± 1.05	6.15 ± 1.24	3.27 ± 1.16*	6.45 ± 1.25	3.18 ± 1.08*	6.25 ± 4.21	2.64 ± 0.59	6.05 ± 1.41

* $P < .5$.
** $P < .01$.