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**Using statistical model selection criteria to discriminate nonsubjectively between hypotheses about physiologic mechanisms underlying experimental observations: a practical example<sup>☆</sup>**

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**Objectives:** Statistical model selection criteria have found widespread use in many areas of science because they essentially provide a quantitative implementation of Occam's razor by balancing the ability of an explanation/model to describe experimental data (goodness of fit) and its complexity (number of parameters). Their use in macroscopic physiologic investigations relevant to critical illness has been limited, however. We therefore aim to demonstrate, using a practical example, how statistical model selection criteria can serve to discriminate, quantitatively, between different hypotheses about physiologic mechanisms if these can be given the form of a mathematical model. We use as an example the data on short-term baroreflex resetting in humans under pharmacologically induced alterations of arterial blood pressure as reported in Fritsch et al (*Am J Physiol.* 1989;256:R549-53), for which we aim to determine which combination of the possible physiologic modifications of baroreflex response, namely, altered heart rate response range, characterized by minimum RR interval (MRR) and RR interval response range (RRR), altered baroreflex setpoint (BSP), and altered baroreflex response slope (BRS) best accounts for the differences in the relationship between RR intervals and carotid artery distending pressures (CDP) under nitroprusside (N), control (C), and phenylephrine (P) treatment.

**Methods:** Hypotheses regarding alterations of baroreflex response after interventions were represented by 16 candidate models based on the standard sigmoidal representation of static, baroreflex-induced heart rate response to carotid arterial distending pressure alterations generated by assuming that each of MRR, RRR, BSP, and BRS could either be identical or vary across interventions, resulting in models with 4 to 12 parameters. After digitizing the experimental data from Fig. 2 in Fritsch et al (1989), we computed maximum likelihood parameter estimates by simultaneously fitting to the N, C, and P data using a Gauss-Newton nonlinear least squares algorithm that was initialized with 1000 random initial guesses from physiologically reasonable parameter ranges for each model, with the objective of minimizing, to the extent possible, the effects of the presence of local minima in this nonlinear optimization problem. For each maximum likelihood estimate, the Bayesian information criterion (BIC) was computed and compared across models. Lower BIC values indicate a better goodness-of-fit/model complexity tradeoff.

**Results:** As expected, the data could be described accurately using the standard sigmoidal model if a sufficient number of free parameters were allowed (in the figure, "V" indicates that the respective parameter was allowed to vary across conditions whereas "F" indicates that it was fixed). Maximum likelihood estimates proved robust against alterations of initial guesses. Residual sum of square errors (RSS) were between the extremes of 358000 ms<sup>2</sup> for

the model that kept all parameters fixed across conditions (top left panel) and 806 ms<sup>2</sup> for the model that allowed different values of all parameters for all conditions (bottom right panel). The minimum BIC of 126.1 was attained for the model where BSP is constant across conditions (RSS 850 ms<sup>2</sup>). The second lowest BIC was 129.98 for the model keeping RRR and BRS fixed across conditions (RSS 1250 ms<sup>2</sup>). BIC for the simplest model, keeping all parameters fixed across conditions, was 269.47, whereas the most complex model, which allowed all parameters to vary across conditions, attained a BIC of 131.25.

**Conclusions:** Model selection using BIC suggests that, under the assumption that both the sigmoidal model of baroreflex response and the statistical assumptions on which BIC is based are valid, the most plausible hypothesis is that baroreflex setpoint remains constant across conditions in the acute setting experimentally characterized by Fritsch et al, whereas MRR, BRR, and BRS are subject to alterations. This is physiologically plausible because teleologically, there is no reason for acute changes in blood pressure to alter the target blood pressure of the physiologic control system, whereas neural as well as neurohumoral factors such as catecholamine secretion (in induced hypotension) or its suppression (in induced hypertension) are certain to alter heart rate responses. Changes in pressure are also known to directly alter the characteristics of baroreceptor response, possibly accounting for BRS alterations. These observations clarify the observations of Fritsch et al regarding the shift of baroreflex operational point and may inform future quantitative descriptions of baroreflex adaptation. Methodologically, statistical model selection criteria such as the BIC offer an attractive approach to arrive at a nonsubjective, quantitative discrimination between hypotheses regarding physiologic mechanisms underlying experimental observations if the competing alternatives can be formulated quantitatively using mathematical models.

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**Are we listening to music or noise? Use of the Lyapunov exponent for comprehensive assessment of heart rate complexity during hemorrhage in sedated conscious miniature swine**

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**Objectives:** Application of tools from nonlinear dynamics for calculation of changes in heart rate complexity assumes presence of deterministic chaotic trends in the investigated data. Calculation of the largest Lyapunov exponent (LLE) is a standard method for confirmation of whether such trends are present and is used to characterize the level of chaos in complex physiologic systems. We sought to evaluate the utility of LLE for that purpose during severe pump-controlled exponential hemorrhagic shock.

**Methods:** Electrocardiogram was recorded from 4 conscious sedated (versed) pigs during baseline followed by a 1-hour-long hemorrhage phase during which 60% of estimated blood volume was withdrawn via a computer-controlled exponential bleeding protocol, followed by resuscitation with Hextend to a target systolic pressure of 65 mm Hg. Datasets consisting of 1024 data points were used to calculate

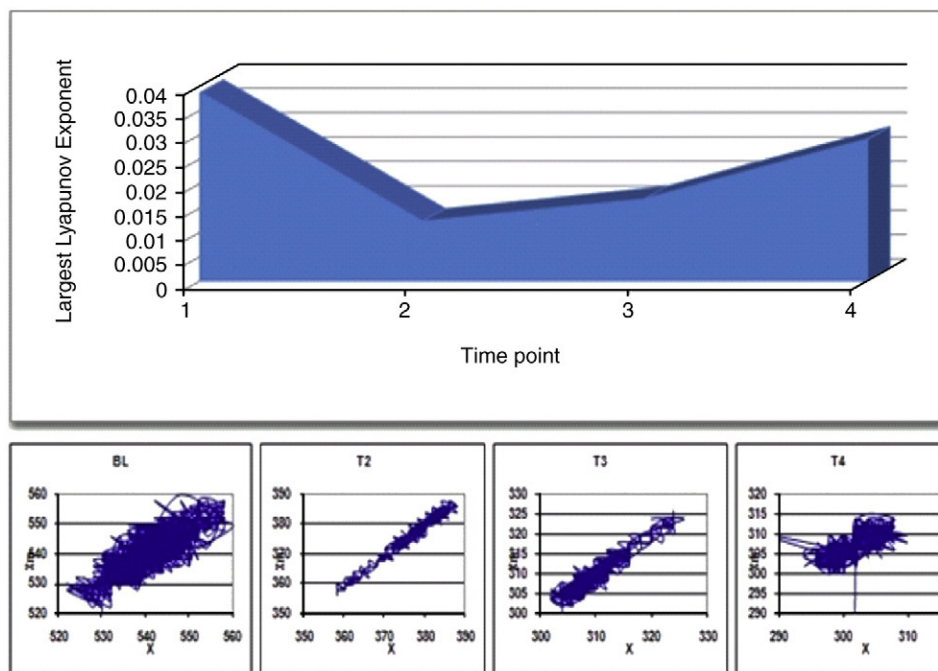
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Variables/time point	T1	T2	T3	T4
SAP	133 ± 4	42 ± 8 ***	36 ± 8 ***	77 ± 3 **
RRI	759 ± 46	601 ± 45	428 ± 43 **	435 ± 39 **
LLE	0.04 ± 0.008	0.01 ± 0.003 **	0.02 ± 0.004 *	0.03 ± 0.009
SampEn	1.50 ± 0.19	1.26 ± 0.10	1.42 ± 0.07	1.43 ± 0.17
ApEn	1.27 ± 0.12	1.19 ± 0.06	1.29 ± 0.04	1.28 ± 0.10
FDCL	1.81 ± 0.07	1.63 ± 0.05	1.72 ± 0.03	1.74 ± 0.07
StatAv	0.92 ± 0.05	0.98 ± 0.05	1.0 ± 0.02	0.88 ± 0.09

\*  $P < .05$ .

\*\*  $P < .01$ .

\*\*\*  $P < .001$ .



the LLE at baseline (T1), at middle of bleeding (T2), at end bleeding (T3), and after resuscitation (T4). The LLE was calculated using the method of Rosenstein (1992). Briefly, the method includes estimation of the mean period using fast Fourier transform; next, the attractor is reconstructed using the method of delays, finding the nearest neighbor to each point in the time series. The LLE measures the average divergence along the trajectories of nearest neighbors and fits a least squares line to the average  $\ln(\text{divergence})$  vs time function. The slope of the line is the LLE. In addition, systolic arterial pressure (SAP), R-to-R interval (RRI), sample entropy (SampEn), approximate entropy (ApEn), fractal dimensions by curve lengths (FDCL), and stationarity (StatAv) were calculated over 800-beat data sets at the same time points. SAS v 12 was used to perform a one-way analysis of variance with repeated measures. Time points were compared with baseline using Dunnett adjustment.

**Results:** See table. SAP, RRI, and LLE decreased. StatAv was high throughout the study.

**Conclusions:** Although there was a significant decrease in LLE, the positive values during hemorrhagic shock and resuscitation indicate that deterministic chaos persisted in the R-to-R interval time series during

the experiment and that use of tools from nonlinear dynamics was appropriate. These findings suggest the utility of LLE as a signal “quality-control measure” and a “measure of chaos” in comprehensive analysis of heart rate complexity during hemorrhage.

Upper panel in figure shows changes in LLE over time. Lower panel shows appearance of the attractor.

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#### A compartmental model reveals a mechanism for misregulation of neutrophil trafficking in sepsis<sup>☆</sup>

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