

COMMENT OPEN



Monitoring chaos at the cot-side

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Intraventricular hemorrhage (IVH) affects ~10–20% of preterm infants born before 30 weeks of gestation.¹ Severe IVH is associated with an increased risk of death and life-long neurodevelopmental disorders such as cerebral palsy² and cognitive, behavioral, and learning difficulties.³ Early detection is a major challenge as more than half of IVH cases are clinically silent, and although some cases present with seizures, many have relatively subtle symptoms.⁴ Being able to identify fetuses or neonates at risk of and determine the temporal profile of IVH in real time would be important to understand the windows for prevention or therapeutic intervention.

Scahill et al. in this issue investigated whether sample entropy (SampEn), a non-linear domain measure of the irregularity in heart rate variability (HRV), could predict intraventricular hemorrhage (IVH) and mortality risk in preterm infants within the first 24 h of life.⁵ In a cohort of 389 preterm infants, a total of 29 developed IVH grade 3 or 4, and 31 infants died. Using the open-source PhysioNet cardiovascular toolbox and a logistic regression prediction model to predict links between SampEn, IVH, and mortality, they found a significant correlation with eventual mortality as early as 4 h of life and with severe IVH by 24 h. At 96 h, when it performed best, the combination of SE with the clinical model yielded an area under the curve (AUC) of 0.9 and above for all three outcome groups and performed better than the clinical model alone.

This study examined the pragmatic discriminative value of SampEn but did not seek to understand the physiological meaning behind the measure. SampEn, first introduced by Richman and Moorman (2000), is a metric of entropy in HR signals.⁶ Entropy reflects the level of irregularity and complexity based on the uncertainty within a signal. Technically, SampEn helps to quantify the conditional probability that two sequences of m points in an epoch of length N remain similar when one consecutive point ($m + 1$) is added within a tolerance of r .⁷ Complexity is related to, but distinct from the variability measured by other (linear) HRV measures of the time and frequency domains.⁸ In the context of cardiovascular regulation, the complexity of HR times series is postulated to reflect the capability of the cardiovascular system to adapt to transient stressors and demands of an ever-changing environment.⁹

It is important to appreciate that the patterns measured by SampEn are often not easily observable to the human eye. Thus, there are two possible interpretations of the patterns observed in this study. First, that breakdown of the physiological inputs that drive HR may lead to unphysiologically regular patterns, as observed in the first ~4–8 h of life (low SampEn) or uncorrelated,

irregular random signals, as observed between 24 and 96 h (high SampEn). These two grades of outcomes, one regular and the other random, are actually indicators of low complexity compared to signals taken from a healthy system.¹⁰ Paradoxically, high SampEn may also imply greater complexity, as complex systems inherently exhibit some irregularity. In the future, alternative non-linear measures like detrended fluctuation analysis (DFA) or newer entropy measures (e.g., fuzzy entropy, entropy rate or other measures that are time-scale-sensitive or probe different embedding dimensions) might offer better differentiation of these features.^{11,12} Nevertheless, these encouraging results strongly suggest that the evolution of FHRV over time can help detect IVH. Indeed, an important question for future studies would be whether the early signature of SampEn suppression extends into the intrapartum or even antenatal periods.

Other potential practical limitations should be considered. SampEn is easily affected by signal artefacts (noise, outliers), which can lead to significant variations in entropy values.⁷ While the authors addressed noise concerns, SampEn is highly parameter-dependent, and incorrect or inconsistent parameter selection can lead to significant changes in the resulting calculated entropy. Pincus and colleagues suggested the standardization of r within the range of 0.1 to 0.25 times the standard deviation of the time-series signal.¹³ Subsequent studies suggest that the r range cannot be easily generalized across datasets.^{14,15} An inappropriate choice of r can lead to the so-called ‘flip-flop’ effect, where results differ dramatically and can be statistically unstable, due to its inherent dependence on the Heaviside function. This two-state signal classifier dichotomizes signal vectors into either “dissimilar” or “similar” without any intermediary states.¹⁴ Further, the present study employed linear regression to prevent overfitting.⁵ While this is a valid approach, it assumes a linear relationship between predictors and HRV, which is not always true for complex physiological systems like HRV.

These observations suggest that future studies should include additional measures as well as SampEn to help predict IVH. More recent methods of measuring entropy have tried to address the technical limitations of SampEn, including so called Fuzzy entropy, Permutation entropy, Distribution entropy and Bubble entropy.^{11,12} Although they sound esoteric, all are readily available through open-source toolboxes.¹⁶ Alternatively, there is growing evidence that HR patterns measured by the highly comparative time series analysis (HCTSA)¹⁷ can predict sepsis¹⁸ and cerebral palsy¹⁹ in preterm and term neonatal populations; this approach includes multiple time, frequency, and non-linear domain measures.

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Overall, this study indicates great potential of open-source software to measure HRV as a screening tool for detecting and tracking the evolution of IVH. Further studies are now needed to better understand the optimal approach.

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