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HRnV-Calc: A Software for Heart Rate n-Variability and Heart Rate Variability Analysis

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Summary

Variation of the time interval between a consistent point in time of each heartbeat (generally related to ventricular electrical activation), known as heart rate variability (HRV) (Rajendra Acharya et al., 2006), has been proven by numerous studies to be a useful indicator of physiological status (Ernst, 2017; Rajendra Acharya et al., 2006). Thanks to its non-invasive nature and strong connection to the autonomic nervous system (ANS) (Ernst, 2017; Rajendra Acharya et al., 2006), HRV has been adopted to study a wide range of diseases and clinical conditions, which include myocardial infarction (Buccelletti et al., 2009), sudden cardiac death (Melillo et al., 2013), diabetes (Kudat et al., 2006), renal failure (Ranpuria et al., 2008), sepsis (Bohanon et al., 2015), seizure (Giannakakis et al., 2019), and cancer (De Couck & Gidron, 2013). In addition, the emergence of wearable devices with heart monitoring capabilities has also allowed researchers to study the above-mentioned medical conditions in real-world settings (Perez et al., 2019), as well as in non-clinical applications such as sports (Dong, 2016), stress (Taelman et al., 2009), and sleep monitoring (Stein & Pu, 2012).

A variety of HRV metrics can be derived from the heartbeat time sequence known as the inter-beat interval (IBI), or the R-to-R peak interval (RR interval or RRI). Such sequences are often extracted from biomedical signals such as electrocardiograms (ECG) and photoplethysmograms (PPG). It is believed that a decrease of complexity in HRV is associated with an increase in both morbidity and mortality (Ernst, 2017; Rajendra Acharya et al., 2006). To qualify and quantify the complexity, various conventional HRV metrics in linear and nonlinear domains (Shaffer & Ginsberg, 2017) have been established to reflect the dynamic of HRV (Rajendra Acharya et al., 2006; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). However, the exact mechanism regulating HRV is not perfectly clear in every detail (Ernst, 2017; Rajendra Acharya et al., 2006). Some of recent developments in HRV have been mainly focused on nonlinear metrics such as variants of approximate entropy (ApEn) and sample entropy (SampEn) (Kamal et al., 2020; Lee & Choi, 2018; C. Liu et al., 2013; Sassi et al., 2015).

Despite progress in HRV metrics research, the representation of RRI upon which HRV is based has rarely been examined. Cysarz et al. (2000) proposed a binary symbolization of

RRI, which combined with ApEn provides new information about the normal heart period regularity. The multiscale entropy (MSE) metrics (Costa et al., 2002) calculate SampEn on multiscale coarse-gained series derived from RRI to reflect the nonlinear behavior of the heart on multiple time scales. To generalize the averaging multiscale approach, N. Liu et al. (2020) proposed heart rate n-variability (HRnV) that utilizes sliding and stridden summation windows over RRI to obtain new RRI-like intervals denoted as RR_nI and RR_nI_m. Using these novel RRI representations, new HRnV metrics can be calculated with conventional HRV analysis metrics, providing an entire family of new metrics, and potentially additional insights into the dynamics and long-term dependencies of the original RRI, making HRnV complementary to the conventional HRV analysis. Research has shown that HRnV improves the accuracy of triage for patients with chest pain (N. Liu et al., 2020) and sepsis (N. Liu et al., 2021). However, full potentials and physiological meaning of HRnV require broader collaboration between researchers and clinicians in various settings and applications. As such, an open and standard software package for HRnV analysis is essential to facilitate further research on HRnV and its possible variations.

Statement of need

There is an abundance of HRV software tools for commercial and non-commercial use, including Kubios HRV (Tarvainen et al., 2014), ECGlab (Vicente et al., 2013), ARTiiFACT (Kaufmann et al., 2011), RHRV (Rodríguez-Liñares et al., 2008), and RR-APET (McConnell et al., 2020). However, none of them is suitable for incorporating HRnV analysis. Moreover, these tools provide inconsistent results, making comparisons between research impossible (Vest et al., 2018). Since HRnV shares some common processing methods with conventional HRV analysis, it is natural to develop the HRnV package based on existing benchmarked software. We therefore developed an open-source HRnV software, HRnV-Calc, based on the PhysioNet Cardiovascular Signal Toolbox (PCST) (Vest et al., 2018). Compared to other HRV freeware, the PCST is standardized and well-documented. More importantly, the PCST is an open-source HRV software suite which has gone through rigorous testing and benchmarking in both technical and clinical settings. Based on the fully functional HRV command-line code provided by the PCST, HRnV-Calc has integrated graphical user interfaces (GUIs) that enable manual inspection and correction of RRI extraction from ECG signals, flexible configuration, and batch-processing, in a step-by-step manner. Its inherent functions support the analysis of both HRnV and conventional HRV metrics with enhanced usability. Therefore, HRnV-Calc not only facilitates new methodological developments, but also provide clinicians and researchers with transparent and easily accessible HRnV and HRV analyses.

Basic Usage

This section provides a non-exhaustive walkthrough of the features and functionalities offered by HRnV-Calc.

The HRnV method for alternative RRI representation is a unique and the main feature implemented in HRnV-Calc. HRnV utilizes sliding and stridden summation windows on the original RRI, resulting in new RR_nI and RR_nI_m intervals (n and m are parameters for HRnV), which can then be fed into conventional HRV analysis to calculate corresponding HR_nV and HR_nV_m metrics. For clarification, the term 'HRnV' refers to the name of the method (i.e., heart rate n-variability), while HR_nV and HR_nV_m refer to the derived metrics based on RR_nI and RR_nI_m intervals, respectively.

HRnV-Calc is primarily operated using its step-by-step GUIs, which include four main interfaces: (1) Data Loader, (2) QRS Detection & Edits (QDE) viewer, (3) HR_nV_m Setting viewer, and (4) HR_nV_m Results Display. A typical workflow using HRnV-Calc is illustrated in Figure 1.

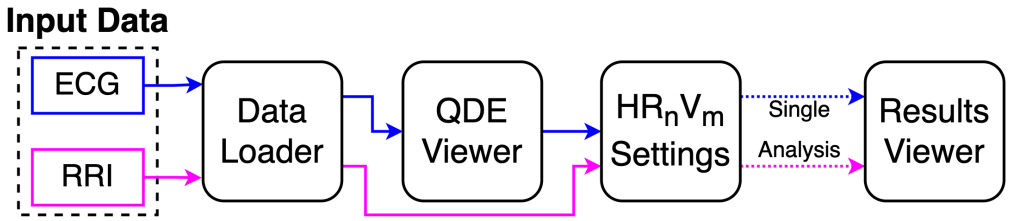

Figure 1: Typical workflow of HRnV-Calc

The initial GUI of HRnV-Calc is Data Loader, which provides basic settings for users to begin HRV/HRnV analyses. Users may choose to perform analysis on a single file or multiple files as batch-processing. Currently, HRnV-Calc supports ECG and RRI inputs in the format of free text and CSV.

Since the QRS peak detection of ECG is crucial for subsequent HRnV and HRV analysis, especially in clinical settings, the QDE viewer is designed to configure and inspect QRS detection on ECG inputs interactively.

The HR_nV_m Setting viewer is used to configure HRnV and HRV analyses. Users may specify the n and m parameters for HRnV analysis and other configurations to process the input signal.

Once the HRnV or HRV analysis is configured, HRnV-Calc will automatically save all analysis results under the user-specified directory in the Excel spread sheet format. In addition, HRnV-Calc will also display the results of a single HR_nV_m analysis for rapid examination of the analysis results.

References

Bohanon, F. J., Mrazek, A. A., Shabana, M. T., Mims, S., Radhakrishnan, G. L., Kramer, G. C., & Radhakrishnan, R. S. (2015). Heart rate variability analysis is more sensitive at identifying neonatal sepsis than conventional vital signs. *AMERICAN JOURNAL OF SURGERY*, *210*(4), 661–667. https://doi.org/10.1016/j.amjsurg.2015.06.002

Buccelletti, E., Gilardi, E., Scaini, E., Galiuto, L., Persiani, R., Biondi, A., Basile, F., & Silveri, N. G. (2009). Heart rate variability and myocardial infarction: Systematic literature review and metanalysis. *Eur Rev Med Pharmacol Sci*, *13*(4), 299–307. https://www.ncbi.nlm.nih.gov/pubmed/19694345

Costa, M., Goldberger, A. L., & Peng, C. K. (2002). Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett*, *89*(6), 068102. https://doi.org/10.1103/PhysRevLett.89.068102

Cysarz, D., Bettermann, H., & van Leeuwen, P. (2000). Entropies of short binary sequences in heart period dynamics. *Am J Physiol Heart Circ Physiol*, *278*(6), H2163–72. https://doi.org/10.1152/ajpheart.2000.278.6.H2163

De Couck, M., & Gidron, Y. (2013). Norms of vagal nerve activity, indexed by heart rate variability, in cancer patients. *CANCER EPIDEMIOLOGY*, *37*(5), 737–741. https://doi.org/10.1016/j.canep.2013.04.016

Dong, J. G. (2016). The role of heart rate variability in sports physiology. *Exp Ther Med*, *11*(5), 1531–1536. https://doi.org/10.3892/etm.2016.3104

Ernst, G. (2017). Heart-rate variability—more than heart beats? *Front. Public Health*. https://doi.org/10.3389/fpubh.2017.00240

Giannakakis, G., Tsiknakis, M., & Vorgia, P. (2019). Focal epileptic seizures anticipation based on patterns of heart rate variability parameters. *COMPUTER METHODS AND PROGRAMS IN BIOMEDICINE*, *178*, 123–132. https://doi.org/10.1016/j.cmpb.2019.05.032

Kamal, S. M., Babini, M. H., Krejcar, O., & Namazi, H. (2020). Complexity-based decoding of the coupling among heart rate variability (HRV) and walking path. *FRONTIERS IN PHYSIOLOGY*, *11*. https://doi.org/10.3389/fphys.2020.602027

Kaufmann, T., Sütterlin, S., Schulz, S. M., & Vögele, C. (2011). ARTiiFACT: A tool for heart rate artifact processing and heart rate variability analysis. *Behavior Research Methods*, *43*(4), 1161–1170. https://doi.org/10.3758/s13428-011-0107-7

Kudat, H., Akkaya, V., Sozen, A. B., Salman, S., Demirel, S., Ozcan, M., Atilgan, D., Yilmaz, M. T., & Guven, O. (2006). Heart rate variability in diabetes patients. *J Int Med Res*, *34*(3), 291–296. https://doi.org/10.1177/147323000603400308

Lee, D. Y., & Choi, Y. S. (2018). Multiscale distribution entropy analysis of short-term heart rate variability. *ENTROPY*, *20*(12). https://doi.org/10.3390/e20120952

Liu, C., Li, K., Zhao, L., Liu, F., Zheng, D., Liu, C., & Liu, S. (2013). Analysis of heart rate variability using fuzzy measure entropy. *Comput Biol Med*, *43*(2), 100–108. https://doi.org/10.1016/j.compbiomed.2012.11.005

Liu, N., Chee, M. L., Foo, M. Z. Q., Pong, J. Z., Guo, D., Koh, Z. X., Ho, A. F. W., Niu, C., Chong, S.-L., & Ong, M. E. H. (2021). Heart rate n-variability (HRnV) measures for prediction of mortality in sepsis patients presenting at the emergency department [Journal Article]. *PLOS ONE*, *16*(8), e0249868. https://doi.org/10.1371/journal.pone.0249868

Liu, N., Guo, D., Koh, Z. X., Ho, A. F. W., Xie, F., Tagami, T., Sakamoto, J. T., Pek, P. P., Chakraborty, B., Lim, S. H., Tan, J. W. C., & Ong, M. E. H. (2020). Heart rate n-variability (HRnV) and its application to risk stratification of chest pain patients in the emergency department. *BMC Cardiovasc Disord*, *20*(1), 168. https://doi.org/10.1186/s12872-020-01455-8

McConnell, M., Schwerin, B., So, S., & Richards, B. (2020). RR-APET - heart rate variability analysis software. *Comput Methods Programs Biomed*, *185*, 105127. https://doi.org/10.1016/j.cmpb.2019.105127

Melillo, P., De Luca, N., Bracale, M., & Pecchia, L. (2013). Classification tree for risk assessment in patients suffering from congestive heart failure via long-term heart rate variability. *IEEE J Biomed Health Inform*, *17*(3), 727–733. https://doi.org/10.1109/jbhi.2013.2244902

Perez, M. V., Mahaffey, K. W., Hedlin, H., Rumsfeld, J. S., Garcia, A., Ferris, T., Balasubramanian, V., Russo, A. M., Rajmane, A., Cheung, L., Hung, G., Lee, J., Kowey, P., Talati, N., Nag, D., Gummidipundi, S. E., Beatty, A., Hills, M. T., Desai, S., … Apple Heart Study, I. (2019). Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med*, *381*(20), 1909–1917. https://doi.org/10.1056/NEJMoa1901183

Rajendra Acharya, U., Paul Joseph, K., Kannathal, N., Lim, C. M., & Suri, J. S. (2006). Heart rate variability: A review. *Med Biol Eng Comput*, *44*(12), 1031–1051. https://doi.org/10.1007/s11517-006-0119-0

Ranpuria, R., Hall, M., Chan, C. T., & Unruh, M. (2008). Heart rate variability (HRV) in kidney failure: Measurement and consequences of reduced HRV. *Nephrol Dial Transplant*, *23*(2), 444–449. https://doi.org/10.1093/ndt/gfm634

Rodríguez-Liñares, L., Vila, X. A., Méndez, A. J., Lado, M. J., & Olivieri, D. (2008). RHRV: An r-based software package for heart rate variability analysis of ECG recordings. *In 3rd Iberian Conference in Systems and Information Technologies (CISTI 2008)*.

Sassi, R., Cerutti, S., Lombardi, F., Malik, M., Huikuri, H. V., Peng, C. K., Schmidt, G., & Yamamoto, Y. (2015). Advances in heart rate variability signal analysis: Joint position statement by the e-cardiology ESC working group and the european heart rhythm association co-endorsed by the asia pacific heart rhythm society. *Europace*, *17*(9), 1341–1353. https://doi.org/10.1093/europace/euv015

Shaffer, F., & Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Front Public Health*, *5*, 258. https://doi.org/10.3389/fpubh.2017.00258

Stein, P. K., & Pu, Y. (2012). Heart rate variability, sleep and sleep disorders. *Sleep Med Rev*, *16*(1), 47–66. https://doi.org/10.1016/j.smrv.2011.02.005

Taelman, J., Vandeput, S., Spaepen, A., & Van Huffel, S. (2009). *Influence of mental stress on heart rate and heart rate variability* (Vol. 22, pp. 1366–1369). ISBN: 978-3-540-89207-6

Tarvainen, M. P., Niskanen, J. P., Lipponen, J. A., Ranta-Aho, P. O., & Karjalainen, P. A. (2014). Kubios HRV–heart rate variability analysis software. *Comput Methods Programs Biomed*, *113*(1), 210–220. https://doi.org/10.1016/j.cmpb.2013.07.024

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J*, *17*(3), 354–381. https://doi.org/10.1161/01.CIR.93.5.1043

Vest, A. N., Da Poian, G., Li, Q., Liu, C., Nemati, S., Shah, A. J., & Clifford, G. D. (2018). An open source benchmarked toolbox for cardiovascular waveform and interval analysis. *Physiol Meas*, *39*(10), 105004. https://doi.org/10.1088/1361-6579/aae021

Vicente, J., Johannesen, L., Galeotti, L., & Strauss, D. G. (2013). ECGlab: User friendly ECG/VCG analysis tool for research environments. *Computing in Cardiology 2013*, 775–778. http://www.cinc.org/archives/2013/pdf/0775.pdf