Appendix 3

Interrelation between ΔS^{shuf} and σ/μ in the case of IID

If we consider Q_k, where $Q_k \geq 0, k = 1, 2, \ldots N$, we obtain the quantities

$$p_k = Q_k / \sum_{l=1}^{N} Q_l,$$

which satisfy the necessary conditions[1]: $p_k \geq 0, \sum_{k=1}^{N} p_k = 1$ to be considered as point probabilities. We then define[2–4] the moments of the natural time $\chi_k = k/N$ as

$$\langle \chi^q \rangle = \sum_{k=1}^{N} (k/N)^q p_k$$

and the entropy

$$S \equiv \langle \chi \ln \chi \rangle - \langle \chi \rangle \ln \langle \chi \rangle,$$

where

$$\langle \chi \ln \chi \rangle = \sum_{k=1}^{N} (k/N) \ln(k/N) p_k.$$

The effect of the time reversal operator[5] on Q_k is obtained by $\mathcal{T} p_k = p_{N-k+1}$, and, similarly, the time-reversed entropy $\mathcal{T} S (\equiv S_-)$ is obtained by the same formula as S but by using p_{N-k+1} instead of p_k.

The relevant expressions for evaluating S and S_-, when a window of lenght $i (= N)$ is sliding pulse by pulse through a time series, are given in Appendix 2 deposited in the same directory as this file.

Here, we consider the case when Q_k are independent and identically distributed (IID) positive random variables. It then follows that the expectation value $\mathrm{E}(p_k) = \mathrm{E}[Q_k / \sum_{l=1}^{N} Q_l]$ of p_k equals $1/N$:

$$\mathrm{E}(p_k) = \frac{1}{N}. \quad (1)$$

Equation (1) results from the fact that, since Q_k are IID, we have:

$$\mathrm{E}[\sum_{k=1}^{N} Q_k / \sum_{l=1}^{N} Q_l] = 1 = N \mathrm{E}(p_k).$$

For the purpose of our calculations, the relation between the variance of p_k,

$$\mathrm{Var}(p_k) = \mathrm{E}[(p_k - 1/N)^2],$$

and the covariance of p_k and p_l,

$$\mathrm{Cov}(p_k, p_l) = \mathrm{E}[(p_k - 1/N)(p_l - 1/N)],$$

is of central importance. Using the constraint $\sum_{k=1}^{N} p_k = 1$, leading to $p_k - 1/N = \sum_{l \neq k}(1/N - p_l)$, and the fact that Q_k are IID, we obtain

$$\mathrm{E}\left[(p_k - 1/N)^2\right] = \mathrm{E}\left[(p_k - 1/N)\sum_{l \neq k}(1/N - p_l)\right] = -(N-1)\mathrm{E}\left[(p_k - 1/N)(p_l - 1/N)\right].$$

Thus, we get

$$\mathrm{Cov}(p_k, p_l) = -\frac{\mathrm{Var}(p_k)}{N-1}. \tag{2}$$

The N-dependence of $\mathrm{Var}(p_k)$ is obtained from

$$\mathrm{Var}(p_k) = \frac{1}{N^2}\mathrm{E}\left[\left(\frac{NQ_k}{\sum_{l=1}^{N} Q_l} - 1\right)^2\right], \tag{3}$$

where the quantity $\mathrm{E}[(NQ_k/\sum_{l=1}^{N} Q_l - 1)^2]$ is *asymptotically* N-independent. The latter arises as follows: If $\mathrm{E}(Q_k) = \mu$ and $\mathrm{Var}(Q_k) = \sigma^2 (< \infty)$, as a result of the central limit theorem[6], we have $\mathrm{E}(\sum_{k=1}^{N} Q_k/N) = \mu$ and $\mathrm{Var}(\sum_{k=1}^{N} Q_k/N) = \sigma^2/N$. The latter two equations, for large enough N imply that

$$\mathrm{E}[(NQ_k/\sum_{l=1}^{N} Q_l - 1)^2] \approx \mathrm{E}[(Q_k/\mu - 1)^2] = \sigma^2/\mu^2.$$

Thus, Eq.(3) becomes

$$\mathrm{Var}(p_k) = \frac{\sigma^2}{N^2\mu^2}. \tag{4}$$

Let us first study $\mathrm{E}[S - \mathcal{T}\mathcal{S}] = \mathrm{E}(S) - \mathrm{E}(\mathcal{T}S)$ for which we intuitively expect that it equals zero for positive IID Q_k. Indeed, we have that

$$\mathrm{E}(S) = \mathrm{E}\left[\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{N}\right)p_k - \sum_{k=1}^{N}\frac{k}{N}p_k\ln\left(\sum_{l=1}^{N}\frac{l}{N}p_l\right)\right] \tag{5}$$

and

$$\mathrm{E}(\mathcal{T}S) = \mathrm{E}\left[\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{N}\right)p_{N-k+1} - \sum_{k=1}^{N}\frac{k}{N}p_{N-k+1}\ln\left(\sum_{l=1}^{N}\frac{l}{N}p_{N-l+1}\right)\right]. \tag{6}$$

The result of Eq.(5) depends on $\mathrm{Var}(p_k)$ and $\mathrm{Cov}(p_k, p_l)$ (see Ref.[7]), whereas that of Eq.(6) on $\mathrm{Var}(p_{N-k+1})$ and $\mathrm{Cov}(p_{N-k+1}, p_{N-l+1})$. In view of the fact that both $\mathrm{Var}(p_k)$ and $\mathrm{Cov}(p_k, p_l)$ are independent of k and l (see Eqs.(2) and (4) above), we have

$$\mathrm{E}(\mathcal{T}S) = \mathrm{E}(S)$$

and moreover[7]:

$$\mathrm{E}(S) = \mathrm{E}(\mathcal{T}S) = \sum_{k=1}^{N} \frac{k}{N^2} \ln\left(\frac{k}{N\overline{\chi}}\right) - \frac{\sigma^2}{(N-1)\mu^2}\left(\frac{\overline{\chi^2}}{\overline{\chi}} - \overline{\chi}\right), \tag{7}$$

where $\overline{\chi} = \sum k/N^2 = (1+1/N)/2$ and $\overline{\chi^2} = \sum k^2/N^3 = (1+1/N)[1+1/(2N)]/3$.

We now turn to the variance of $\Delta S \equiv S - \mathcal{T}S$ defined by

$$\sigma^2[\Delta S] \equiv \mathrm{E}\left\{[S - \mathcal{T}S - \mathrm{E}(S-\mathcal{T}\mathcal{S})]^2\right\} = \mathrm{E}\left[(S-\mathcal{T}S)^2\right],$$

in view of Eq.(7), which is of primary importance in ECG. We have that

$$\begin{aligned} \sigma^2[\Delta S] &= \mathrm{E}\left[(S-\mathcal{T}S)^2\right] = \mathrm{E}\left[\{[S-\mathrm{E}(S)] - [\mathcal{T}S - \mathrm{E}(\mathcal{T}S)]\}^2\right] \\ &= \mathrm{E}\left\{[S-\mathrm{E}(S)]^2\right\} + \mathrm{E}\left\{[\mathcal{T}S - \mathrm{E}(\mathcal{T}S)]^2\right\} - 2\mathrm{E}\left\{[S-\mathrm{E}(S)]\,[\mathcal{T}S-\mathrm{E}(\mathcal{T}S)]\right\} \\ &= 2\left[\delta S^2 - \mathrm{E}\left\{[S-\mathrm{E}(S)]\,[\mathcal{T}S-\mathrm{E}(\mathcal{T}S)]\right\}\right], \end{aligned} \tag{8}$$

where we used the fact that $\delta S^2 \equiv \mathrm{E}\left\{[S-\mathrm{E}(S)]^2\right\}$ (originally defined in Ref.[8], see also Ref.[7]) remains unchanged under time reversal for the same reasons as $\mathrm{E}(S) = \mathrm{E}(\mathcal{T}S)$. The term $\mathrm{E}\left\{[S-\mathrm{E}(S)]\,[\mathcal{T}S-\mathrm{E}(\mathcal{T}S)]\right\}$ can be evaluated in a way similar to the one used in Ref.[7]. Namely, we add and subtract the term $\sum_{k=1}^{N} \frac{k}{N} p_k \ln\overline{\chi}$ from S and the term $\sum_{k=1}^{N} \frac{k}{N} p_{N-k+1} \ln\overline{\chi}$ from $\mathcal{T}S$. We then expand the resulting logarithmic terms $\ln[1+\sum_{l=1}^{N}\frac{l}{N}(p_l - \frac{1}{N})/\overline{\chi}]$ and $\ln[1+\sum_{l=1}^{N}\frac{l}{N}(p_{N-l+1} - \frac{1}{N})/\overline{\chi}]$ to first order in $(p_l - \frac{1}{N})$ and $(p_{N-l+1} - \frac{1}{N})$, respectively. This leads to

$$\begin{aligned} \mathrm{E}\left\{[S-\mathrm{E}(S)]\,[\mathcal{T}S-\mathrm{E}(\mathcal{T}S)]\right\} &= \mathrm{E}\left\{\left[\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{eN\overline{\chi}}\right)\left(p_k - \frac{1}{N}\right) - \right.\right. \\ &- \left.\frac{1}{\overline{\chi}}\sum_{k=1}^{N}\frac{k}{N}(p_k - \frac{1}{N})\sum_{l=1}^{N}\frac{l}{N}(p_l - \frac{1}{N}) + \frac{\sigma^2}{(N-1)\mu^2}\left(\frac{\overline{\chi^2}}{\overline{\chi}} - \overline{\chi}\right)\right] \times \\ &\times \left[\sum_{k'=1}^{N}\frac{k'}{N}\ln\left(\frac{k'}{eN\overline{\chi}}\right)\left(p_{N-k'+1} - \frac{1}{N}\right) - \right. \\ &- \frac{1}{\overline{\chi}}\sum_{k'=1}^{N}\frac{k'}{N}(p_{N-k'+1} - \frac{1}{N})\sum_{l'=1}^{N}\frac{l'}{N}(p_{N-l'+1} - \frac{1}{N}) + \\ &+ \left.\left.\frac{\sigma^2}{(N-1)\mu^2}\left(\frac{\overline{\chi^2}}{\overline{\chi}} - \overline{\chi}\right)\right]\right\}, \end{aligned} \tag{9}$$

where $e = 2.7182\ldots$ is the base of natural logarithms. *If* we assume that the distribution of

Q_k is *symmetric* around μ and keeping up to the first order in σ^2/μ^2, Eq.(9) simplifies to

$$\begin{aligned} \mathrm{E}\left\{[S-\mathrm{E}(S)]\left[\mathcal{T}S-\mathrm{E}(\mathcal{T}S)\right]\right\} &= \mathrm{E}\left\{\left[\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{eN\overline{\chi}}\right)\left(p_k-\frac{1}{N}\right)\right]\times\right. \\ &\times \left.\left[\sum_{k'=1}^{N}\frac{k'}{N}\ln\left(\frac{k'}{eN\overline{\chi}}\right)\left(p_{N-k'+1}-\frac{1}{N}\right)\right]\right\}. \end{aligned} \qquad (10)$$

Now, using Eqs.(2) and (4), we obtain

$$\mathrm{E}\left\{\left(p_k-\frac{1}{N}\right)\left(p_{N-k'+1}-\frac{1}{N}\right)\right\} = \frac{\sigma^2}{(N-1)N\mu^2}\delta_{k,N-k'+1} - \frac{\sigma^2}{(N-1)N^2\mu^2}, \qquad (11)$$

where $\delta_{l,m}$ is Kronecker's delta (equal to 1 if $l=m$, and 0 otherwise). Substituting Eq.(11) into Eq.(10), we finally find that

$$\begin{aligned} \mathrm{E}\left\{[S-\mathrm{E}(S)]\left[\mathcal{T}S-\mathrm{E}(\mathcal{T}S)\right]\right\} &= \frac{\sigma^2}{(N-1)\mu^2}\left\{\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{eN\overline{\chi}}\right)\times\right. \\ &\times \frac{N-k+1}{N}\ln\left(\frac{N-k+1}{eN\overline{\chi}}\right)\frac{1}{N} - \\ &- \left.\left[\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{eN\overline{\chi}}\right)\frac{1}{N}\right]^2\right\} \end{aligned} \qquad (12)$$

Using now Eq.(A21) of Ref.[7] for δS^2, i.e.,

$$\delta S^2 = \frac{\sigma^2}{(N-1)\mu^2}\left\{\sum_{k=1}^{N}\left(\frac{k}{N}\ln\frac{k}{eN\overline{\chi}}\right)^2\frac{1}{N} - \left[\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{eN\overline{\chi}}\right)\frac{1}{N}\right]^2\right\}, \qquad (13)$$

we obtain

$$\begin{aligned} \sigma^2[\Delta S] &= \frac{2\sigma^2}{(N-1)\mu^2}\left[\sum_{k=1}^{N}\left(\frac{k}{N}\ln\frac{k}{eN\overline{\chi}}\right)^2\frac{1}{N}-\right. \\ &- \left.\sum_{k=1}^{N}\frac{k}{N}\ln\left(\frac{k}{eN\overline{\chi}}\right)\frac{N-k+1}{N}\ln\left(\frac{N-k+1}{eN\overline{\chi}}\right)\frac{1}{N}\right] \end{aligned} \qquad (14)$$

Equation (14) reflects that, when a window of length $i(=N)$ is sliding through the randomly shuffled Q_k of an ECG, the following relation holds

$$\sigma[\Delta S_i^{shuf}] = \frac{\sigma}{\mu}\sqrt{f(i)}, \qquad (15)$$

where

$$f(i) = \frac{2}{i-1}\left[\sum_{k=1}^{i}\left(\frac{k}{i}\ln\frac{k}{ie\overline{\chi}}\right)^2\frac{1}{i} - \sum_{k=1}^{i}\frac{k}{i}\ln\left(\frac{k}{ie\overline{\chi}}\right)\frac{i-k+1}{i}\ln\left(\frac{i-k+1}{iN\overline{\chi}}\right)\frac{1}{i}\right].$$

In the main text, the numerator in the measure $N_i \equiv \sigma[\Delta S_i^{shuf}]/\sigma[\Delta S_i]$ was calculated on the basis of Eq.(15).

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