Impact of pulsatility on the ensemble orderliness (approximate entropy) of neurohormone secretion

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Veldhuis, J. D., M. L. Johnson, O. L. Veldhuis, M. Straume, and S. M. Pincus. Impact of pulsatility on the ensemble orderliness (approximate entropy) of neurohormone secretion. Am J Physiol Regulatory Integrative Comp Physiol 281: R1975–R1985, 2001.—Regular patterns of neurohormone secretion are driven by underlying pulsatile and subordinate (feedback sensitive) dynamics. Measures of time-series orderliness, e.g., the approximate entropy (ApEn) statistic (Pincus SM. Proc Natl Acad Sci 88: 2297–2301, 1991), vividly discriminate pathological and physiological patterns of hormone release. To investigate how specific pulsatility features impact regularity estimates, we have examined the sensitivity of the ApEn metric to systematic variations in the frequency, amplitude, and half-life of simulated neurohormone pulse trains (Veldhuis JD, Carlson ML, and Johnson ML. Proc Natl Acad Sci 84: 7686–7690, 1987) and compared the impact of a high vs. low baseline luteinizing hormone (LH) pattern regularity state mimicking the normal female luteal phase and the young male, respectively. Shortening the interpulse interval length elevated ApEn in both pulsatility models, thereby signifying greater ensemble series irregularity. The frequency sensitivity of ApEn was robust to several complementary renditions of ApEn and to variations in experimental uncertainty, basal (nonpulsatile) LH secretion, and secretory burst amplitude. ApEn rose with increasing hormone half-life, especially in the face of low baseline variability emulated by midluteal LH secretion profiles. High variability of secretory burst amplitude, pulse duration, or interpulse intervals increased ApEn in the more orderly femalelike construct; in the highly irregular malelike LH pulse model, these variability changes had little effect on ApEn. In summary, the ensemble regularity statistic, ApEn, quantifies unequal pattern orderliness in neurohormone pulse trains with minimal dependence on mean pulse amplitude, interpulse baseline, or (subthreshold) sample uncertainty. Thus ApEn monitors changing secretory event frequency and interpulse variability with sensitivity to starting pattern regularity, providing a mechanistic linkage between model evolution and statistical change.

hormone release; statistics; patterns; biomathematics

ENDOCRINE GLANDS direct remote target tissues via pulsatile hormone signals (5, 43). Pulsatility is modulated by feedforward and feedback activity within the neuroendocrine axis (12–14), thereby conferring physiological regulation (46). Such adaptive complexity makes the consequences of altered neurohormone pulsatility and feedback control difficult to calibrate. Indeed, in some pathophysiological contexts, pulsatility quantitation itself becomes challenging (7, 39, 44, 45, 62). Pattern regularity quantification provides a complementary perspective of coupled systems (26, 30, 31). For example, neuroendocrine tumors that disrupt within-axis control markedly impair the serial reproducibility (or subpattern orderliness) of hormone secretion, as quantified by independently validated regularity statistics (7, 42). One such metric, approximate entropy (ApEn) (20), discriminates male and female growth hormone (GH) secretory pattern regularity (8, 17, 24) and identifies more disorderly hormone release profiles in healthy aging individuals (10, 16, 31, 45, 53). However, the degree to which altered feedback and pulse pathophysiology direct differences in ensemble pattern orderliness has not been determined by explicit mathematical model analysis. One recent analysis begins to address this issue by examining the relationship between pulsatility and regularity changes in a basic simulation model comprising a convolved (triangular) input signal and an (exponential) impulse-response function (41).

To explore further how distinct pulsatility features impact the ensemble orderliness of neurohormone time series, we have implemented a broad multiparameter model, which emulates the well-ordered luteinizing hormone (LH) pulse trains typically reported in midluteal-phase women (1) and highly irregular LH pulsing of young men (43). Thereby, we examine the impact of the model platform (e.g., low- vs. high-irregularity ApEn baseline profiles) on ApEn sensitivity to within-series pulsing variability. Our findings indicate the utility of a composite regularity measure in quantifying complex output differences due to specific pulsatility changes. These insights should aid in interpreting potential feedback changes within a neuroendocrine axis independently of pulsatility distinctions and in the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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providing a mechanistic interpretation to ApEn findings in hormone secretory patterns.

METHODS

Convolution integral. Simulated pulsatile neurohormone time series were created exactly as described previously (47, 50, 52). Briefly, trains of discrete pulses are modeled as the integrated output of a secretion function, \( S(z) \), convolved with an elimination function, \( E(t - z) \) (47, 50). \( S(z) \) is defined as the sum of an underlying basal time-invariant (nonpulsatile) secretion rate and a series of secretory bursts of fixed half-duration \( z = 2.354 \times \) the standard deviation (SD) of a Gaussian waveform and variable amplitudes \( A_i \), occurring at times \( T_i \). Here, \( A_i \) and \( T_i \) are independently and identically distributed random normal variables. Variability of pulse amplitude and interval length was defined by corresponding parameter-specific coefficients of variation (CV = SD/mean \( \times 100\% \)) (52, 55). The \( E(t - z) \) function was approximated as a monoeponential elimination process, taken arbitrarily as 50 min (or otherwise as noted) to emulate nominal human LH kinetics (48). The convolution product, \( S(z) \cdot E(t - z) \), was integrated analytically at 0.1-min intervals (52). The resultant time series were discretized to simulate a typical 10-min (or other as indicated) sampling frequency. To incorporate procedural uncertainty, experimental variance was superimposed additively on each synthetic sample replicate value as independently and identically distributed random Gaussian noise at a specified CV (initially 8%) with a minimum (absolute) replicate SD of 0.1 (arbitrary) concentration units (IU/l). Data were synthesized as duplicate within-sample values, the means of which were appraised by ApEn analysis. Any (rare) predicted negative hormone concentrations were regenerated with another iteration. Time series were created for 15 slow-phase half-lives before the resultant 1,440-min (or longer) time segment was analyzed.

One hundred pulse-train realizations with different random seeds were constructed for each ApEn calculation of LH profiles mimicking the midluteal phase of the normal human menstrual cycle (1) and of the healthy young male (43). Corresponding convolution integral parameter sets were used to emulate the high- and low-pulsing regularity states. Common parameters in both models included a half-life of 50 min, mean secretory burst amplitude of 0.3 IU/1 min \( ^{-1} \), and a fixed secretory pulse half-duration of 11.77 min (SD = 5.0 min). The mean interpulse interval length was 360 min (±0% CV) in the female and 60 min (±30% CV) in the male, and independently and identically distributed noise was ±20% and ±80%, respectively. Basal (nonpulsatile) time-invariant LH concentrations were defined as 1.0 (female) and 0 IU/l (male) in the simulated profiles. The foregoing parameter choices approximate the published attributes of LH pulse trains in healthy young midluteal-phase women and normal men (6, 40, 43, 51, 59).

ApEn analysis. ApEn is a model-free regularity measure that quantifies the orderliness of subordinate patterns in mathematical sequences and empirical time series (20, 26, 30). ApEn comprises a two-parameter family of statistics, \( \text{ApEn}(m, r) \), with \( m \) a run length and \( r \) a de facto tolerance width (see Refs. 24 and 31 for practical examples). Normalized ApEn parameters of \( m = 1 \) and \( r = 20\% \) of each series SD were used here, as previously described for various neurohormone profiles of this length (7, 10, 24, 57).

The ApEn statistic monitors sample-by-sample pattern irregularity and is thus distinguished from conventional analyses of pulsatility or circadian rhythmicity. Higher ApEn values denote greater irregularity (or process randomness) of successive time series, as reported for tumoral time series (7, 39, 44, 45, 62); GH patterns in boys during mid- to late puberty and prepubertal children administered sex steroid hormones (4, 57); GH secretion in females compared with males (8, 24, 57); and ACTH, LH, GH, cortisol, testosterone, and insulin time series in aging humans (8, 10, 16, 31, 53).

The distribution of empirically “random” (maximal) ApEn values was determined by 1,000 random shuffles of ordered sample values within each time series. Thereby, ApEn of each “observed” (unshuffled) time series was also evaluated as a mean ratio of observed-to-random ApEn and as a calculated \( z \) score (number of SDs) removed from an empirically maximally random ApEn value (58).

RESULTS

Figure 1 illustrates simulated femalelike (Fig. 1A) and malelike (Fig. 1B) serum LH concentration profiles. More extended 10-min discretized pulse trains are shown for females to highlight the behavior of infradian pulses. Simulation parameter choices included a mean LH secretory burst amplitude of 0.3 IU/1 min \( ^{-1} \) (±0% CV in the female and ±30% CV in the male), a 0 or 1 IU/l basal (female and male) LH concentration, a fixed half-life of 50 min, and 2 or 8% superimposed experimental uncertainty (female and male, respectively) (see METHODS). Higher mean pulse frequencies increased pattern irregularity visually in both sets of simulated time, as quantified further by ApEn analysis. The de facto dependence of ApEn on enforced LH pulse frequency is exemplified in Fig. 1C, wherein a gonadotropin-releasing hormone (GnRH)–deficient patient received fixed intravenous GnRH pulses at three different intervals (data provided by Drs. F. C. Hayes and W. F. Crowley, Jr.).

Figure 2 summarizes the impact on ApEn of varying interpulse intervals (s) in the malelike (baseline more irregular) LH pulse stimulation model using 100 datasets (realizations) per ApEn estimate, on the basis of preliminary comparisons among 10, 30, 100, 300, and 1,000 realizations (not shown). Discretized time series were evaluated at ApEn parameters of \( m = 1 \) and \( m = 2 \) and \( r = 20\% \) (see METHODS). In particular (at constant interpulse variability of ±30%), a higher mean pulsing frequency or, equivalently, a lower interpulse interval consistently reduced ensemble series regularity. We see this in three ways: 1) a rise in ApEn (Fig. 2, top); 2) an increase in the mean ratio of observed-to-random ApEn values (Fig. 2, middle); and 3) a fall in the ApEn \( z \) score, denoting the number of SDs by which an observed ApEn value diverged from empirically maximally random ApEn (Fig. 2, bottom). The malelike (more orderly baseline) LH pulse simulation model analogously showed strong ApEn dependence on mean pulsing frequency (not shown).

The foregoing relationships were evident for ApEn vector lengths of \( m = 1 \) and \( m = 2 \) and for several appropriate choices of the ApEn threshold (\( r \) values, Fig. 3A). Statistically inappropriate choices of \( r \) (e.g., 2 or 200%) and progressive undersampling of the data series (e.g., a 30-, 60-, or 90-min sampling interval) corrupted the sensitivity of ApEn to changes in mean pulse frequency (Fig. 3B).
Figure 4 depicts the influence on ApEn of the convolved hormone elimination rate based on simulated femalelike and malelike LH profiles (half-life, Fig. 4A). More prolonged LH half-lives elevated ApEn for both gender simulations. ApEn was largely independent of mean secretory burst amplitude (IU·1⁻¹·min⁻¹, Fig. 4B), whereas increasing secretory burst SD (min, Fig. 4C) reduced ApEn. ApEn was also unaffected by changes in underlying basal (time invariant, non pulsatile) LH concentrations (0.03, 0.1, 0.3, and 1.0 IU/l, not shown).

Figure 5 depicts the effect on ApEn of heightening the variability of interburst interval, secretory burst amplitude, and burst half-duration over a broad range of CVs at otherwise fixed mean parameter values (see METHODS). Higher variability of pulse amplitudes elevated ApEn in the more orderly femalelike LH simulations (Fig. 5A), yet it had very small effect on ApEn for small and moderate variability and somewhat reduced ApEn given very high (30%–100% CV) variation in the highly irregular LH release malelike setting (Fig. 5B). Figure 6 illustrates typical simulation outputs. Thus the degree of baseline
irregularity (low vs. high) modulates ApEn responses to markedly altered parameter variability.

DISCUSSION

The present detailed pulse simulation analyses delineate baseline-, sample uncertainty-, and pulse amplitude-independent (i.e., scale invariant) properties of the ApEn statistic and document strong pulse frequency, hormone half-life, and parameter variability sensitivity of this regularity metric. Comparisons between pulse models emulating low and high baseline irregularity of LH secretory profiles typifying the human midluteal phase in the female and the normal young male, respectively, unveiled an impact of intrinsic model structure on ApEn evolution to pulse perturbations.

The relative independence of ApEn from variations in baseline and pulse amplitude in simulated neurohormone pulse trains is consistent with the theoretically predicted scale and translation invariance of this regularity measure in simpler coupled numerical systems (19, 29, 30). ApEn contrasts were also largely insensitive to underlying random experimental uncertainty (noise) below the ApEn threshold. The foregoing three empirically validated features of ApEn would suggest the utility of this metric in comparing complex neurohormone time series with nonidentical pulse amplitudes, baselines, and (subthreshold) noise levels.

Further simulations established that mean pulsing frequency governs ensemble orderliness of the neurohormone time series (Fig. 2). In particular, abbreviating the interpulse interval length elevated ApEn independently of model choice, thereby denoting greater irregularity of subordinate subpatterns. Thus a pattern-sensitive statistic such as ApEn should offer a complementary means to discriminate among pulse trains with unequal mean pulsing frequencies, even when discrete peak detection would seem difficult (e.g., serum LH pulse profiles driven at higher frequencies; see Fig. 1). Indeed, the latter issue arises commonly in neurohormone tumoral secretion profiles, as exemplified by the adenomatous release of GH, ACTH, prolactin, and aldosterone (7, 18, 35, 39, 44, 45). Analogously, the highly irregular secretory output of GH in the female compared with male rat and human and of insulin and LH in aging and diabetic humans makes traditional peak identification difficult in these diverse settings (4, 14, 16, 24).

From the perspective of the experimentalist, the present pulse train simulations also highlight the relevance of appropriately chosen ApEn parameters and sampling intervals. First, in relation to ApEn compar-

Fig. 2. Impact of varying mean interpulse interval length on the ApEn(m,r) estimate of time-series ensemble regularity. Pulse trains simulating malelike LH time series were created as described in Fig. 1. ApEn was calculated at r = 20% and m = 1 and m = 2 (top). The ApEn ratio was computed as the mean ratio of each observed ApEn value to that of 1,000 randomly shuffled representations of the same series (middle). The ApEn z score was defined as the number of SDs that each observed ApEn value was removed from empirically maximally random (shuffled) ApEn (bottom) (see METHODS). Mean interpulse interval lengths are indicated on the y-axis (logarithmic scale). Each ApEn data point is the mean ± SD (N = 100 simulated series).

irregularity (low vs. high) modulates ApEn responses to markedly altered parameter variability.
ison vector lengths ($m = 1$ and $m = 2$), subpattern reproducibility can be viewed as aggregating contiguous pair ($m = 1$) or triple ($m = 2$) distributions from an entropy-based perspective. As established earlier on empirical grounds, neurohormone time series of a typical length of 50–300 data points are often distinguished vividly by $\text{ApEn} m = 1 (4, 7, 24, 27, 34, 39, 44, 53, 54, 58)$. In contrast, $\text{ApEn} m \geq 2$ is relevant to discriminate more intensive and/or extended data series ($19, 29, 30, 33$). The ApEn contrasts observed here illustrate this analytic distinction. Second, in relation to choice of ApEn threshold ($r$, normalized as a per-

Fig. 4. Impact of systematic variations in mean hormone half-life ($A$) and secretory burst amplitude ($B$) and SD ($C$) on the estimation of ApEn($m$, $r$) in the orderly femalelike LH pulsatility model ($A–C$, top) and the highly irregular malelike LH pulsatility model ($A–C$, bottom). Data are presented otherwise as described in legend of Fig. 2.
The percentage of the individual series SD), \( r \) less than two- to threefold of the within-sample random experimental variability discriminated pulsing differences with high reliability. Third, in relation to sampling frequency, simulations reinforced the importance of adequate sampling integrity of neurohormone pulse trains to distinguish series orderliness. This observation follows, inasmuch as ApEn is a family of regularity statistics parameterized on \( m \) and \( r \), as well as \( N \) (series length). Accordingly, an earlier empirical analysis was used to define minimal series length(s) required to separate tumoral and normal GH and ACTH secretory patterns with high (75%) sensitivity and specificity (27). Given the complexity of secretory disruption in pathophysiology (5, 43), relevant simulation-based analyses may provide a complementary approach to mapping discriminative ApEn parameters in selected experimental and clinical contexts.

Further analyses corroborated an earlier finding and theoretical prediction of ApEn sensitivity to the convolved impulse-response (elimination) function. The mathematical basis for and biological implications of this relationship have been discussed (41). The present data corroborate the foregoing expectation in both low and high baseline regularity models. Accordingly, to the extent that secretory calculations do not introduce additional (technique dependent) variability in the derivative time series, applying ApEn to secretory output may enhance statistical contrasts. This inference was illustrated earlier by ApEn calculations of LH release profiles obtained by sampling the ovariectomized ewe at a central hypophalampituitary portal site (to achieve predominantly secretion estimates) vs. a more peripheral jugular venous site (yielding an admixture of secretion, dilution, and elimination) (32).

The present biomathematical simulations of neurohormone pulse trains also establish that pulsing variability is an important non-frequency-dependent ApEn determinant. In the femalelike LH pulse model of highly regular baseline profiles (low initial ApEn), increased interpulse variability elevated ApEn progressively. In the malelike LH pulse model of more disorderly baseline release, increased pulse-to-pulse variability at any given mean pulse frequency, amplitude, or duration either had minimal effect on ApEn (for CV < 30%) or reduced ApEn (for CV > 30%). These platform-dependent features of ApEn evolution highlight the importance of primary physiological model structure. Clinical applications of ApEn likewise document system-specific ApEn contrasts in normal and pathological states; e.g., disease reduces ApEn of electrocardiographic and parathyroid hormone oscillations, whereas pathological secretion of LH, ACTH, GH, prolactin, cortisol, aldosterone, testosterone, and insulin elevates ApEn (2, 7–9, 11, 15, 22, 25, 27, 31, 34–39, 44, 45, 49, 53, 56, 58, 60–62). Whereas the present data do not bear directly on these diverse relationships, we can infer that the baseline state of model variables itself influences model output during strong perturbations.

Fig. 5. Effect of changing the degree of variability (CV) of individual pulse attributes, i.e., interpulse interval length, secretory burst amplitude, and SD, on ApEn\((m,r)\). A: more orderly femalelike LH pulse model typical of the midluteal phase of the normal human menstrual cycle. B: more irregular malelike LH pulse model (see METHODS).
The ApEn statistic quantifies the degree of order-dependent subpattern regularity in a time series (19, 23, 30). In addition, the variability of a particular pulse attribute (such as the amplitude, duration, or interpulse waiting time) can be considered in an order-independent manner, e.g., as designated by the CV of that parameter value. From an intuitive perspective, very high variability of (nonsuccessive) pulse amplitudes and/or interpulse intervals within an already disorderly time series (such as the malelike LH profiles simulated here) could confer greater ensemble regularity due to the occasional emergence of unusually large, wide, and/or more isolated pulses, manifesting the statistical bias discussed below.

Inasmuch as ApEn can discriminate the variability of pulse attributes in two series with comparable mean frequencies (above), we suggest that the mechanistic basis for pulsatility disruption in pathophysiology could be dissected further by quantifying the variability of discrete pulse features. For example, one could appraise both order-dependent (ApEn) and order-independent (CV of mean) variability of pulse amplitude and interpulse interval length in a time series. As illustrated in Fig. 7A, testosterone administration elevated ApEn of more disorderly 24-h serum GH concentration profiles in older but not young men without changing GH pulse frequency (3). Androgen treatment concurrently blunted GH pulse-mass variability (lower CV of the set of GH pulse-mass values) without changing GH interpulse interval variability [pooled mean ± SD (CV), 50 ± 4.9%]. In extension, the higher ApEn ratio of the ordered sequence of successive GH pulse-mass (but not interpulse interval) values induced by testosterone supplementation in older men uncovers heightened irregularity of ad seriatim pulse amplitudes (Fig. 7B). According to these insights, one might infer that exogenous testosterone in the aged male evokes greater nonuniformity of successive hypothalamic signaling inputs and/or pituitary somatotrope responsiveness, thereby explaining more disorderly patterns of GH roles.

**Perspectives**

The primary message in this study is that one can infer a direct mechanistic relationship between param-
parameter changes in a model of secretory dynamics and associated changes in output signal irregularity. Herein, we have used model parameter specifications based on two quite distinct LH secretory settings (emulating young men and midluteal women) to derive a number of such inferences. Most inferences were common to both settings, e.g., the ApEn increases with increasing half-life and with increasing pulse frequency. A few inferences were more state specific, e.g., the ApEn response to increased variability in burst amplitude or frequency. Although the choice of LH is strictly representative, we expect the aforementioned qualitative inferences to hold under much broader conditions, so that those conclusions common to both settings herein will hold under very general conditions, for a large plurality of hormones and physiological states. Conversely, in a few settings, it is imperative to know, at least qualitatively, the approximate state of the underlying physiological model to draw valid inferences between ApEn and parameter space.

We emphasize that the general qualitative conclusions drawn above (e.g., increasing half-life increases ApEn) should be interpreted as valid for models such as those used herein, and in likelihood for structurally similar models, but not necessarily for all model and network formulations. The putative utility of the preceding analysis is that the underlying model structure is a well-established first-order approximation of true hormonal dynamics and incorporates a number of biological properties and interrelationships that are (somewhat) specific to hormonal secretory dynamics. Thus the present paper goes beyond the more generally oriented and reductionist models, which link ApEn to its mechanistic relationship to parameter changes in broader, yet in some senses simpler, settings (20, 41).

The present model interpretations are consistent with those seen in previous studies under comparable settings, e.g., in comparing the effects of increasing pulse frequency and/or amplitude variation for a (somewhat) regular baseline time series. Our results using female LH simulations (Fig. 5A) are consistent with those of both Refs. 20 and 41 and with the general theme that increasing the SD of underlying pulse amplitude or frequencies increases ApEn given a low-to-moderate ApEn baseline.

Several statistical issues must be noted. Although generally ApEn with \( m = 1 \) and with \( m = 2 \) will provide similar qualitative findings, in some settings (e.g., series lengths \( N < 300 \) points) \( m = 1 \) is preferred, whereas for longer series \( (N > 300) \) \( m = 2 \) generally gives sharper distinctions. The tradeoffs, discussed more theoretically elsewhere (21, 26), are between the slightly greater reproducibility of ApEn with \( m = 1 \) for shorter series vs. the sharper probabilistic description provided by the \( m = 2 \) statistic. In statistical “boundary” contexts, this distinction is often relevant. Note that in Fig. 3A with the choice of \( r = 6\% \) (a generally inappropriate \( r \)), the resultant \( m = 1 \) ApEn curve agrees more with the primary finding (as seen in the appropriate \( r = 20\% \) panel). Similarly, in Fig. 3B, at 20-min simulated sampling, the \( m = 2 \) ApEn curve differs directionally from the 5- and 10-min sampling curves, reinforcing that for these sampling rates, \( m = 1 \) is the superior choice for valid statistical interpretation. However, in the vast majority of settings, including virtually all other figures here, the qualitative conclusions from \( m = 1 \) and \( m = 2 \) runs are common.

The relatively flat ApEn curves in Fig. 5B deserve special mention. In Fig. 5B, we investigated the effects on ApEn of increasing process variation (increasing pulse amplitude or frequency variation) atop a highly irregular (“males”) baseline series and observed minimal ApEn change, except at extreme levels of variation. The technical issue is that data are already nearly maximally irregular (33); thus there is negligible statistical room for further ApEn increases, with a resultant apparent asymptote. This illustrates the consider-

![Fig. 7. A: reduced variability (lower CV) of 24-h (deconvolution estimated) growth hormone (GH) secretory pulse-mass values in healthy older (relative to young) men administered testosterone enanthate (200 mg im) weekly for 3 wk to stimulate pulsatile GH secretion (3). The latter intervention elevated ApEn of the serum GH concentration time series akin to the recognizably more irregular malelike pattern of GH release in the rat and human (4, 5, 24, 54, 57) without altering GH secretory burst frequency (see DISCUSSION). B: increased irregularity (elevated ApEn ratios) of successive GH pulse-mass values in older men supplemented with testosterone as above (3). P values denote the results of unpaired parametric testing. Data are means ± SE (n = 8 subjects).](http://ajpregu.physiology.org/DownloadedFromHttp://ajpregu.physiology.org/)
characteristics and serial irregularity (ApEn) of resultant representative hormonal time series from a well-established, multiparameter model of secretory dynamics.

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