Optimal Data Analysis
2013, Vol. 2, Release 1 (September 27, 2013), 37-42

2155-0182/11/$3.00

Modeling Individual Reactivity in Serial Designs: Changes in Weather and Physical Symptoms in Fibromyalgia

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This note criticizes current statistical convention, and discusses and illustrates appropriate statistical methodology for investigating the relationship between weather and individual symptoms.

Our interest in this specific problem derives from findings of content analysis of free-form comments, voluntarily recorded by 339 American patients with fibromyalgia (FM) over a 14-week period, using our web-based, interactive, self-monitoring and feedback system (SMART) during its alpha test as a behavioral CAM intervention for FM.[1] Of 2,215 discrete comments made in total, 1,732 (78%) involved symptoms, and 244 (11%)—*one of nine comments made*—noted weather-related phenomena, often remarking that worse weather exacerbated symptoms, or improved weather reduced symptoms. A total of *twenty-two independent comments* stated that specific weather events triggered *clinically significant symptom flares.*

A high prevalence of weather-related symptoms exists even among people well-adapted to challenging climatic conditions: in a study of cold-related complaints of 8,723 Finns aged 25-64 years, for example, 75% reported decreased mental or physical performance, and 33% reported musculoskeletal pain.[2] It is intuitive that extreme weather is especially challenging to people with FM, as diminished concentration and physical ability, and musculoskeletal pain, are *prevalent* symptoms of FM.

Concurrent research conducted in the USA has studied the relationship between changes in weather and symptoms of FM patients. A survey of 94 patients found prevalent reporting of modulation of aches and pains by weather factors, especially among young patients.[3] A study of 84 patients found subjects believed weather predominantly affected their musculoskeletal symptoms, and that higher weather sensitivity is associated with greater functional impairment and psychological distress.[4] And, an internet survey of 2,596 patients reported the most common aggravating factors for symptoms were weather changes, emotional distress, insomnia, and strenuous activity.[5]

International research findings have been consistent. For example, 17 patients in Argentina completed surveys assessing the presence and features of spontaneous daily pain occurring over a one-year period, and same-day barometric pressure and temperature were significant correlates of pain ratings.[6] A retrospective cross-sectional study

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of 955 rheumatic patients in Portugal reported FM patients were strongly influenced by weather change.[7] And, nearer the equator where meteorological variation is lower, a clinical interview of 15 female patients in Brazil revealed that climate variation was uniformly considered to be a trigger event, as well as a modulating factor, for pain.[8]

Prospective research also examined the relationship between weather and symptoms of FM patients. In a one-month study of pain ratings and changes in daily weather conditions in Israel, pain was significantly related to barometric pressure for 11 patients.[9] Longitudinal survey assessment of seasonal symptoms was conducted for 1,424 patients with rheumatic disease in the USA, and were associated with seasonal weather differences measured for periods up to 24 years; number and severity of weather-related symptoms were elevated in patients with FM.[10] Finally, daily pain ratings of 55 female patients in Norway were recorded for 28 days, and related to weather parameters and a composite weather variable using time series analysis: no association between same- or prior-day weather and pain was found, but *post hoc* analysis found patients with less than ten years of symptoms had significantly greater weather sensitivity than patients with longer illness.[11]

In light of the personal, family and societal costs of FM,[12] the abundant qualitative evidence that weather change plays an important precipitating and modulating role in FM symptom flares, and the paucity of actionable findings, further study in this area is clearly warranted. In this context the present note considers the appropriate statistical methodology for assessing the relationship between weather and individual symptoms.

GHA and Physical Symptoms

Prior research in this area studied barometric pressure, but for this example we instead use 500 mb geopotential height anomaly (GHA) measured in meters. This height is proportional to the mean temperature of the air column extending from a point on the Earth's surface to approximately 18,000 feet: the 500 mb GHA is the amount above or below mean height for that point and time. GHA is more appropriate than barometric pressure presently due to the broader geographic expanse of the features GHA defines, given the imprecise information available to us concerning the location of subjects and the time that their symptoms occurred.[13]

Patient symptom ratings were obtained via the SMART system: individuals rate (maximum frequency=daily basis) their condition across time on ten prevalent FM symptoms, using 10-point Likert-type scales (mean=3.5 entries/patient/week).[1] Review of the database produced a total of 11 individual patient records which met three inclusion criteria: ratings unequivocally organized by entry date (database requires sequential entry); weather conditions unequivocally identified on entry date (data-base includes state of residence); and statistical power analysis mandated a minimum of 48 ratings.[1]

Table 1 gives the Kendall tau b correlation coefficient (and *p*) for GHA and symptom, both assessed on the same day, *separately by patient*. Tau was selected because distributional assumptions underlying parametric methods were unsupported empirically. Considering the inherent non-stationary non-linearity of both daily symptoms and GHA across time, tau found a surprisingly high number of statistically reliable, ecologically non-trivial associations among symptoms and weather. As expected, the number of reliable coefficients decreased with sample size: statistical power is reduced, and smaller Ns yield lower variability, limiting the maximum magnitude that correlation indices may attain.[14] Seven of 11 pa-

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tients (64%) had at least one reliable association, and 9 of 11 patients (82%) had at least one marginal association. Patient 5 showed extreme reactivity to GHA (every symptom except gastrointestinal was associated with GHA), and patients 6 and 11 had no GHA reactivity. Comparing symptoms, mental focus and depression were most reactive (three patients each had statistically reliable associations). Associations were generally strongest for depression, and gastrointestinal difficulties were least reactive to GHA. For patient 5 the coefficient for sleep difficulties was twice as large as for any other patient for this symptom. Results show *GHA influenced symptom(s) of most people studied.*

Table 1: Single-Case Statistical Analysis of the Relationship between GHA and Physical Symptoms for 11 FM Patients

Patient #	1	2	3	4	5	6	7	8	9	10	11
State of Residence	ID	AZ	OR	CA	MN	TX	OH	TN	TN	CA	PA
Days Reported	99	98	89	79	75	62	59	56	52	52	51
Pain	0.09	0.14	-0.02	0.11	-0.20	-0.06	-0.01	-0.15	-0.18	0.09	-0.05
	0.31	0.08	0.84	0.20	0.007	0.51	0.91	0.17	0.10	0.40	0.61
Stiffness	0.10	-0.01	-0.08	0.22	-0.17	-0.01	0.01	0.12	-0.18	0.05	-0.14
	0.24	0.87	0.32	0.008	0.022	0.93	0.93	0.91	0.08	0.68	0.19
Fatigue	-0.02	-0.01	-0.07	0.06	-0.20	-0.05	-0.20	0.09	-0.12	0.01	0.08
	0.78	0.92	0.39	0.51	0.008	0.60	0.05	0.36	0.25	0.99	0.46
Mental Focus	-0.06	0.17	0.17	0.09	-0.27	0.07	-0.13	0.19	-0.17	0.06	-0.01
	0.48	0.04	0.03	0.31	0.001	0.48	0.20	0.08	0.11	0.60	0.93
Memory	-0.03	0.10	0.16	-0.03	-0.24	0.10	-0.13	0.12	-0.13	0.01	0.03
	0.72	0.23	0.05	0.73	0.002	0.29	0.21	0.27	0.19	0.99	0.78
Anxiety	-0.27	0.01	0.08	0.12	-0.19	0.11	0.01	-0.04	0.01	0.04	0.06
	0.002	0.96	0.32	0.18	0.018	0.25	0.94	0.73	0.94	0.73	0.61
Depression	-0.30	0.21	-0.07	-0.07	-0.38	0.10	-0.01	0.11	-0.11	-0.01	-0.05
	0.001	0.01	0.42	0.39	0.001	0.31	0.99	0.33	0.30	0.97	0.65
Gastro-intestinal	-0.14	-0.04	0.06	0.06	0.05	0.07	-0.01	-0.15	-0.14	-0.22	0.02
	0.07	0.63	0.49	0.47	0.55	0.49	0.90	0.17	0.19	0.05	0.83
Sleep Difficulties	-0.17	0.06	0.11	-0.01	-0.36	0.04	-0.10	0.18	-0.10	0.07	-0.04
	0.042	0.47	0.21	0.90	0.001	0.68	0.33	0.09	0.33	0.53	0.73

Note: Tabled separately by patient (columns) and symptoms (rows) is Kendall Tau b coefficient (top value in cell) for same-day GHA and the indicated symptom, and the corresponding *p* value (bottom value). State of residence and number of data ratings (days) are indicated in the column heading for each patient. Results in red are reliable (generalized $p \leq 0.05$), and results in blue are marginal (generalized $p \leq 0.10 < 0.05$). For 99 tests of statistical hypotheses, 4.95 "statistically significant" ($p \leq 0.05$) effects are expected by chance: thus the total of 18 reliable effects observed is more than 3.6 times greater than is expected by chance.

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Results also demonstrate that people are not uniform in their responses to the weather, but rather that *one's reaction to weather change is intrapersonal and idiosyncratic*. For example, contrast the reliable *negative* depression coefficient for patient 1, versus the reliable *positive* depression coefficient for patient 2. Note that if the data for these two patients were combined, then the resulting depression coefficient would be: tau=-0.04, $p \leq 0.49$. *Combining the data of these two patients would thus eliminate the effect for depression and mask both effects which in reality existed*. Combining two sets of intrapersonal data can induce many forms of psychometric confounding known as "Simpson's Paradox," and combining more than two data sets can make matters intractably confounded.[15] *The current standard operating methodology in research design and statistical analysis involving symptom data involves combining subjects into groups, a convention which clearly induces paradoxical confounding.*

Predicting Specific Symptoms

Patients sometimes recorded recurring symptoms (e.g., migraine headache) in their SMART comment log. Patient (MN, 75) was selected to demonstrate the use of optimal data analysis in this application. For this patient, when a headache was reported the record (day) was coded *positive for headache*: all other records were coded *negative for headache*. Univariate optimal data analysis[16] (UniODA) was used to predict if the patient was positive or negative for headache on a given day (class variable), based on the GHA value for that day (attribute). Figure 1 illustrates the resulting model.

Figure 1: Headache UniODA analysis

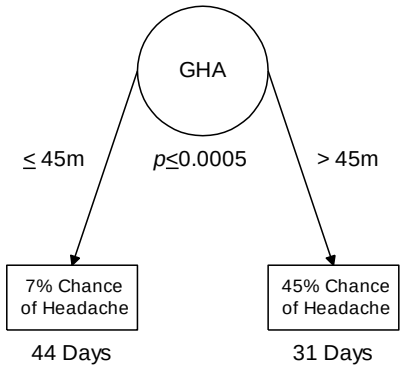
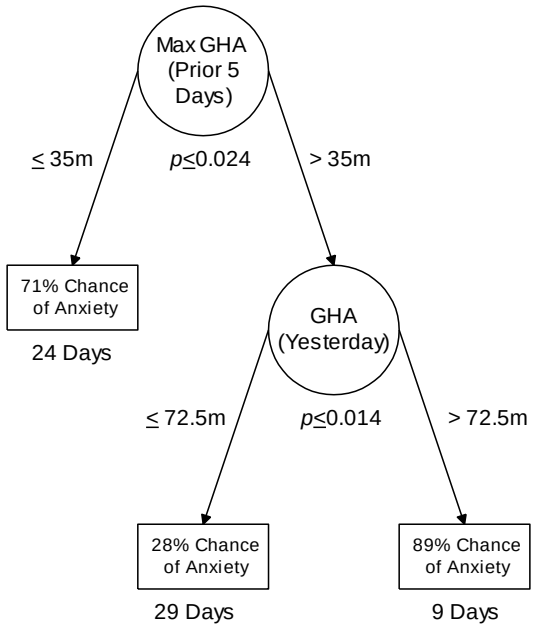


Figure 2: Anxiety CTA Analysis



In Figure 1 the attribute is indicated by the circle; the cutpoint used to predict headache status (identified by UniODA, this threshold maximizes predictive accuracy) is indicated next to arrows (pathways through the model); the exact Type I error rate (*p* value) is given beneath the attribute; and model endpoints are in-

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dicated using rectangles. Endpoints give the likelihood that the patient will report a headache, and the number of days represented by the endpoint. There is more than a 6-fold difference in the likelihood of a migraine for this patient, based simply on whether the GHA value for the day is 45m or less (7% likelihood of headache), versus greater than 45m (45% likelihood).

Hierarchically optimal classification tree analysis (CTA) is an algorithm which chains UniODA models together to produce multivariable non-linear models.[17] In the prior example the patient was *highly reactive* to GHA in tau analysis. In contrast, daily anxiety self-ratings of patient (TX, 62)—who was *nonreactive* to GHA in tau analysis, was selected to illustrate CTA. When the patient recorded anxiety greater than median for her time series, the record (day) was coded *positive for anxiety*. All other records were coded *negative for anxiety*. CTA predicted whether the patient was positive or negative for anxiety on a given day (class variable): weights reflected increasing deviation from median.[13] Attributes available for predicting anxiety for any given day in the patient's time-series were GHA value for that day, the prior day ("yesterday"), and two, three and four days ago, and the minimum and maximum value of GHA over the prior five days. Figure 2 shows the model obtained using automated CTA.[18]

When maximum GHA (prior 5 days) is ≤35m, there is a 71% likelihood the patient will report high anxiety. When maximum GHA (prior 5 days) is >35m *and* GHA yesterday is >72.5m, there is an 89% likelihood the patient will report high anxiety. However, if GHA yesterday is ≤72.5m, there is only a 28% likelihood the patient will report high anxiety. Because this is a *U-shaped* association—anxiety increases as GHA deviates from median, it is thus not surprising that tau—a linear model, failed to identify the effect. In jackknife analysis the CTA model correctly classified 25 of 33 (76%) high anxiety days, and 21 of 29 (72%) low-anxiety days: weighted ESS=57, a relatively strong effect. For this patient the CTA model provides greater than 3-fold improvement in ability to forecast anxiety based on the value of local GHA.

Discussion

The use of optimal statistical methods to create actionable models for predicting individual physical symptoms on the basis of local GHA (in combination with other attributes) is extremely promising. Development of an integrated system capable of producing individually-tailored real-time feedback derived from optimal analysis requires overcoming two engineering challenges: (1) acquisition of valid GHA[13] (and other serial[19]) measures; and (2) acquisition of accurate and timely location and symptom data. The alpha test of an integrated system which overcomes these obstacles is currently underway in our laboratory. Of course, these methods may be applied to the analysis of any serial measure in relation to any binary outcome, and parallel applications are in different stages of planning, design and development in our laboratory as of this writing.

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