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Obtaining More Information from a Contingency Table: Pseudo Markov Chain Analysis

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Introduction

In clinical research, it is of interest to know how a patient's symptoms vary over time after treatment. The problem is typically approached statistically by first calculating the differences in response before and after treatment, and then subjecting the resulting delta to the Wilcoxon/Kruskal-Wallis tests (Rank Sums), a non-parametric version of Student's t-test for independent data [1,2]. In the case of a non-significant response, it is accepted that the treatments have equal activity with a certain degree of probability ($p > .05$). However, this information, although important, is poor in details that could better clarify the effects of treatment. It could happen that the lack of significance is motivated by the fact that both treatments, evaluated separately (Wilcoxon Signed Test, the non-parametric version of Student's t-test for dependent data) [1,2], are actually active and therefore not different from each other, in agreement with the test on delta.

The purpose of this document is to describe a procedure that we have developed, which allows for the recovery of new information from data, including valuable information that the experimenter may not have identified or evaluated for their own studies. The procedure deals with the patient's persistence and migration from one "state" to another - evolving over time - using the method that will be explained below.

Methods

The procedure involves the use of pseudo-Markov chains, which are a type of stochastic process used to model the evolution of a system over time. In the context of clinical research, the system can be thought of as the patient's health status, which can be classified into various states depending on the symptoms experienced.

Using the contingency table obtained from the before-after treatment analysis, the transition probabilities between different states can be estimated using the pseudo-Markov chain approach. The resulting probabilities can provide additional information on the efficacy of the treatments and the likelihood of transitioning between different health states over time.

Taking inspiration from the raw data (Table 1) of a clinical study reported in the International Journal of General Medicine [3], where 50 patients treated with Quercetin were compared with 50 patients treated with Standard, in order to evaluate the effect of Quercetin on symptom frequency such as fever, headache, cough...

Table 1: Frequency of symptoms under two treatments.

Trattamento	Number of symptoms	
	Day 1	Day 7
QP	3	0
QP	2	0
Standard	2	0
QP	1	1
Standard	1	0
…	…	…
Standard	3	0
QP	3	1
Standard	3	1
QP	3	0
QP	4	1
Standard	3	1
Standard	3	1

QP=Quercetin

Excerpt of the experimental data obtained

The authors' conclusions, on the analyzed variable, were: "The Wilcoxon/Kruskal-Wallis test, at the end of the seventh day of treatment, showed an identical response of the groups ($p=0.1789$, table 2)".

Table 2: Wilcoxon/Kruskal-Wallis Test.

1-Way Test, ChiSquare Approximation		
ChiSquare	DF	Prob>ChiSq
1.8067	1	0.1789

Using the pseudo-Markov chain to acquire new information. Analysis of "state" changes

Simplifying, a Markov chain is a process in which the probability of moving from one "state" to another (called transition probability) depends only on the state reached in the previous event. In other words, the process has no memory. However, our technique for generating new information will only borrow the concepts of *state* (Day 1 or 7th day) and *transition* (the passage between the two) from the theory. This is why we talk about "pseudo-Markov chain".

We represent the symptom data reported in table 1 in a transition matrix in which the patient can be in 5 different states, identified, in this case, by 0, 1, 2, 3, 4 symptoms. The initial state (Day 1) is reported in the left column, and the final state of the patient (7th day; table 3a for QP and 3b for Placebo) is reported in the row above. Table 3a illustrates the changes in the frequency of the number of symptoms that each QP patient simultaneously showed at the end of the trial.

Table 3a: Transition of symptoms for the QP group.

	Day 7				
	Count	0	1	2	Total
	1	1	3	0	4
Day 1	2	9	3	0	12
	3	14	11	1	26
	4	2	5	1	8
	Total	26	22	2	50

In the Day 1, column 0 is missing because asymptomatic patients are absent. In the 7th day row, patients with 3 or 4 symptoms were omitted because they were not present.

The evolution of the system for the QP group reaches the following final state (total per row):

- Out of the 4 patients with 1 symptom (count) at Day 1, only one is symptom-free at the 7th day, while 3 do not change their initial symptoms.
- Out of the 12 patients with 2 symptoms at Day 1, 9 have no symptoms at the 7th day, while 3 have only one symptom.
- Out of the 26 patients with 3 symptoms at Day 1, 14 no longer have them, another 11 have only 1 symptom at the 7th day, while another patient migrates to the "state" of 2 symptoms.
- Out of the 8 patients with 4 symptoms at Day 1, 2 eliminate them, 5 reveal only 1 symptom at the 7th day, and 1 patient has 2 symptoms.

The observed cases for the Placebo group highlight the following conclusions:

Table 3b: Transition of symptoms for the Standard group.

	Day 7				
	Count	0	1	2	Total
	1	2	0	0	2
Day 1	2	2	6	1	9
	3	7	21	2	30
	4	1	6	2	9
	Total	12	33	5	50

- Out of the 2 patients with 1 symptom at Day 1, none show symptoms at the 7th day.
- Out of the 9 patients with 2 symptoms at Day 1, 2 have no symptoms at the 7th day, 6 have only one symptom, while one patient has 2.
- Out of the 30 patients with 3 symptoms at Day 1, 7 have no symptoms, 21 have only 1 symptom at the 7th day, while two patients move to the state of 2 symptoms.
- Out of the 9 patients with 4 symptoms at Day 1, 1 has no symptoms, 6 complain of 1 symptom, and 2 others reveal 2 symptoms at the 7th day.

Due to the complexity of the statistical evaluation of the information presented in the previous tables (due to the presence of zeros and frequencies <5), we have devised new subject categories based on the "state" migrations previously discussed:

Healed

Patients who exhibit one or more symptoms at Day 1, but none (0) at Day 7.

Improved

Patients who show a lower number of symptoms at Day 7 than at Day 1.

Unchanged

Patients who show no variation in their symptom frequency between the two periods.

Worsened

Patients with a higher number of symptoms at Day 7 than at Day 1.

Asymptomatic

All patients with the absence of symptoms, both at Day 1 and at Day 7.

We summarize the transition rules applied in Table 4:

Table 4: Transition rules.

		Symptoms at Day 7				
		0	**1**	**2**	**3**	**4**
	0	A	W	W	W	W
	1	H	U	P	W	W
Symptoms	**2**	H	I	U	P	W
at Day 1	**3**	H	I	I	U	W
	4	H	I	I	I	U

A=Asymptomatic, **H**=Healed, **I**=Improved, **U**=Unchanged, **W**=Worsened

Comparison between Day 1 vs Day 7

For QP and Placebo, we create a new and more informative representation of the data (Table 5), which highlights that of the 50 QP patients analyzed, 52% heal, 42% improve, and 6% show no changes in symptom frequency between the beginning and end of the study.

Table 5: Conclusions after pseudo-Markovian analysis.

Count	Standard	QP	Total
% of column			
HEALED	12	26	38
	24.00	52.00	
IMPROVED	37	21	58
	74.00	42.00	
UNCHANGED	1	3	4
	2.00	6.00	
Total	50	50	100

In contrast, of the 50 Pl patients evaluated, 24% heal, 74% improve, and 2% show no changes in symptomatology. The difference in efficacy between the two treatments, absent in the original study, becomes evident when the previous data is subjected to the Chi Square test. The overall evaluation of frequencies in Table 5 favors the QP treatment (Tables 6a and 6b) with p=0.0045 and p=0.0051, respectively for Chiˆ2 according to the likelihood ratio and Chiˆ2 according to Pearson.

Table 6a: Between-group comparison.

P-value Chi^2		
Maximum Likelihood Ratio		
	QP	Standard
QP	1.0000	0.0045
Standard	0.0045	1.0000

Table 6b: Between-group comparison.

P-value Chi^2 (Pearson)		
	QP	Standard
QP	1.0000	0.0051
Standard	0.0051	1.0000

In Table 7, we report new information obtained from the frequencies in Table 5: the Healed are significantly higher in the QP group (52% vs 24%, with p=0.0039 according to Pearson), while the Improved predominate in the Placebo group (74% vs 42%, with p=0.0012, again according to Pearson). No differences were observed in the comparison between Unchanged (p<0.3074).

Table 7: Comparisons between patient typologies.

Maximum Likelihood Ratio		
	QP vs St	Pl vs St
HEALED	0.0036	1.0000
IMPROVED	0.0011	1.0000
UNCHANGED	0.2969	1.0000
Chi^2 Pearson		
	QP vs St	Pl vs St
HEALED	0.0039	1.0000
IMPROVED	0.0012	1.0000
UNCHANGED	0.3074	1.0000
Fisher's Exact Test		
	QP vs St	Pl vs St
HEALED	0.0070	1.0000
IMPROVED	0.0022	1.0000
UNCHANGED	0.6173	1.0000

By juxtaposing the previous Recovered label with the symptoms manifested by the patients (Figures 1 and 2), we ascertain that the QP group had a greater severity at Day 1 than the comparison group due to a higher frequency of symptoms 2 and 3 (89% vs 75%). Despite this initial handicap, the QP treatment was more effective.

Figure 1
N=26 HEALED QP at Day 7
Severity at Day 1 %

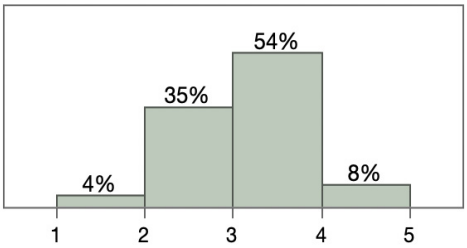
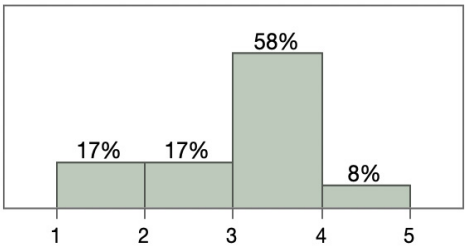


Figure 2
N=12 HEALED Standard at Day 7
Severity at Day 1 %



All statistical procedures were performed on a MacBook Pro computer using the JMP 14 Pro program of the Sas Institute Inc.

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