A Comment on "Adverse Drug Reactions and Avalanches: Life at the Edge of Chaos"

Since the 1970s when chaos theory and fractals started to become widely known, their nonconventional and sometimes heretic results have appealed to a lot of scientists because of their interdisciplinary character and wide applicability.[1-4] Indeed, this transfer of knowledge from mathematics and physics to other fields has been fruitful, and many successful applications can be reported, especially in the biological sciences where apparently these concepts are particularly applicable because of the complexity of the studied systems. However, there have also been a number of controversial applications.[5,6]

Frattarelli[7] studies the population distribution of the severity of adverse drug reactions (ADRs) from data taken from literature. His results conclude that this distribution follows a power-law, a signature of complex systems, providing evidence that ADRs are an inevitable consequence of the undoubtedly complex human body. A very interesting and simple result, had it been correct. However, this report contains several serious misconceptions, which we detail in ascending importance: (1) The power-law found is not well justified, as the fitting is poor; (2) even if a power-law described the data well, it would not imply complexity, as it does not extend several orders of magnitude; and finally (3) such an analysis is not correct for ordinal data of this size. More specifically:

1. In Figure 1A of Frattarelli's article,[7] a fitted line to the data is shown on a log-log plot; however, the line does not fit very well to the data, which clearly seem to concave downward. In fact, it is easy to show that an exponential function, being a straight line on a linear-log plot rather than a log-log one, fits to these data clearly much better, as it is shown in Figure 1. However, even the exponential function is not a correct option because one cannot perform linear regression with ordinal data of this size, as we will discuss below.
2. The physical meaning of the power-law corresponds to the properties of scale invariance, statistical self-similarity, and structure within structure, found in fractals and complex systems.[1,5] For a power-law to be valid in this context, it is necessary to extend over several orders of magnitude, and there has been discussion of how large this range should be to be considered enough, given the fact that physical-biological systems have natural limits.[5] On the other hand, in Frattarelli's article,[7] what we have is an ordinal variable (severity) that extends within half an order of magnitude and, in fact, consists of only 4 consecutive values that correspond to ordered categories. So even if the power-law did fit well to the data, this by no means could give evidence for self-similarity or scale invariance. Also, it cannot be extrapolated beyond the given range, as there can possibly be no greater severity than 4, which corresponds to the fatal state. The latter also compromises the argument that because of the nature of the power-law, ADRs are inevitable, as this considers the asymptotic behavior beyond the fatal state. The limited range of the data is also related to the next point, which is probably the most serious one.
3. Ordinal data, as these analyzed by Frattarelli,[7] are categorical data that are ordered, so one can make statements such as "greater than" or "smaller than," but the interval or the ratio between the classes is not meaningful. Therefore, one cannot say that severity 4 (fatal) is 2 times more severe than severity 2 (nonserious) and 4 times more severe than severity 1 (no reaction). As a result of that, performing regression analysis with ordinal data is not formally correct.[8,9] Also, considering a nonlinear relation, such as the power-law, pronounces even further any discrepancy. Having said that, it is common in some analyses for ordinal variables to be treated as continuous, and there have been arguments that this can be a reasonable approximation, provided that the number of classes is large enough. Berry reads: "It is clearly inappropriate to treat any ordered discrete variable with a small number of values (say, five or fewer) as continuous" (p47).[9] Zipf's law, also quoted in Frattarelli's article,[7] is an example, where a power-law is used to describe the distribution of an ordinal variable, that is, the rank

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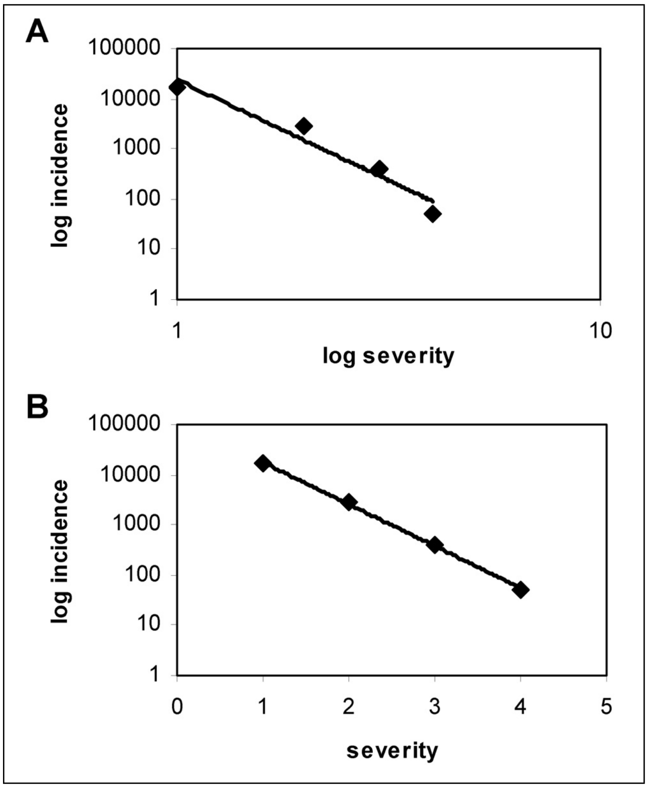

Figure 1. Log-log plot (A) and linear-log plot (B) of incidence versus the severity of adverse drug reactions. See text for the invalid use of regression analysis for both plots. The data were taken from Frattarelli DA. Adverse drug reactions and avalanches: life at the edge of chaos. J Clin Pharmacol. 2005;45:866-871.

of how common a word is, but the number of classes is basically the size of the English dictionary, that is, thousands.

To conclude, Frattarelli[7] uses an attractive idea, which is not implemented in a proper way. In fact, we would not be surprised if ADRs turn out to follow a power-law, if this could be quantified properly; but it is our opinion that Frattarelli's report[7] does not give any evidence toward that direction.

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Author's Response

I am grateful to Drs Dokoumetzidis and Macheras for their letter and thoughtful review of my article, in which they raise 3 interesting points. I will offer my thoughts on each of these.

1. Their first concern was that the data may fit better to an exponential function than to a power one. They rightly observe that the summed data presented in Figure 1a are concave down, which on log-log axes suggests an exponential relation. They are also correct that these summed, meta-analysis data fit an exponential function better (R^2 = .9508 for power versus .994 for exponential).

This was something I was aware of when doing the research for this article. Exponential and power fits were compared for each of the sets of data presented in the original article.[1] As shown in the following table, for the 8 sets of data presented in prospective studies, 5 fit a power function better, and 3 fit an exponential better.

	Power	Exponential
Gurwitz		
Overall	.9536	.8859
Preventable	.8653	.9667
Lazarou		
Bates	.9446	.9435
Miler	.9158	.9907
McKenzie	.969	.9939
Gardner	.9989	.9472
Seidl	.9634	.9543
Schimmel	.9826	.9569

Also, the number of data points that fit a power equation better totaled 235 838 versus 13 286 for an exponential. Given this, all the data in my report were fit to a power function, as the intent was to look for a common process. Although some of the data fit to an exponential function better, they also fit a power equation very well and were highly statistically significant when they did.

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The reason the data in Figure 1a from my report fit an exponential equation better is the largest study included in Lazarou's meta-analysis (Miller et al, representing 59% of the data points) fit an exponential better than a power function, and this bent the data concave down.

Thus, although they are correct in their interpretation of this single graph, I believe that the data overall fit a power function well.

2. The issue of scale invariance over a large range is an important one, but the problem here is more one of graining than of limited range.

They are correct that having more data points, ideally over several orders of magnitude, would be better. But the problem here is one of detection. The unfortunate fact is that there is no precise method for finely grading and separating the majority of adverse drug reactions (ADRs) on the basis of their severity. As a result, there is a coarse-grained set of data with subjective stratifiers such as "mild" or "serious" to work with.

The range presented in these studies, however, is comprehensive. I suggest that the fact that the data points in these studies range from no reaction to fatal implies that the whole possible range of ADRs is represented here. As such, the range presented here is adequate and could extend over several orders of magnitude, if only we had a better means of rating these reactions' severity.

As for the point about the inevitability of ADR relying on extrapolation of data to an asymptote beyond the fatal state, I disagree. Consider the format of a power equation,

$$y = mx^p$$

where y is the dependent variable (in this case the incidence of an ADR), m is a scaling constant related to the "height" of the line, x is the independent variable (in this case severity), and p is the power constant that describes the slope. As I tried to show in my article, this slope is similar across all populations reported, so we can hold p constant. Changes that make ADRs more or less likely will change the value of m and will thus shift the line up or down, respectively. Therefore, *y* will always retain a non-zero value, meaning that the ADR of a chosen severity will occur.

3. Drs Dokoumetzidis and Macheras's third point is the most interesting, and they are absolutely right that the analysis of categorical data as continuous is suboptimal. However, the reference from Berry presented is not definitive in that it does not give any justification or reference as to why "say, five or fewer" is inappropriate or why samples in the thousands are a "reasonable approximation" of categorical to continuous data. I am unfortunately unable to find in the literature any analysis of a method for examining a sample size of categorical data and assessing its suitability for analysis as continuous.

In the absence of this analysis, I wrote a simulation program that generated 1000 iterations of random data sets of 4 or 5 data points (similar to those analyzed in my article), which were then compared against continuous data using a Pearson's correlation coefficient and resultant *P* value. For a 4-point model, the mean Pearson's correlation was .945 ± .04, with 54.5% of runs significant at $P < .05$. For a 5 category test, the mean correlation was about the same (.946 ± .04), and 91.9% of runs were significant at $P < .05$.

This is far short of a formal proof, but I think it suggests that the data interpretation in the overall set from Gurwitz (having a 5-point data set) is reasonably solid. It is more equivocal with the 4-point set in the other data sets. Given the >50% chance that this is a reasonable approximation at a significance of .05, I still think there is something meaningful to be derived from this interpretation.

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