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Modeling human health behavior with a new index that measures connectivity

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ABSTRACT

Objective: Health behavior is an important determinant of health. Adherence to medication and abstinence from harmful substances are two critical health behaviors. Although conceptually related, both are assessed using disparate measures. The goal of this study was to develop and test a new index, gamma, which models health behavior by quantifying the connectedness of discrete incidents of health behavior.

Study design and setting: We derive gamma from first principles and use it to reanalyze data from a published trial of treatment for alcohol use disorders. We model a primary endpoint, changes in binge drinking, using gamma and a traditional measure: change in number of monthly binges. The original trial was conducted in an urban hospital emergency department in the U.S.

Results: Incorporating gamma into the model provided additional insights into the relationship between the intervention and long-term changes in drinking.

Conclusion: Gamma provides an additional tool to model the effects of interventions on outcomes in trials of substance use interventions or medication adherence. Gamma measures the pattern of behavior and may increase the explanatory power of models assessing differences between various treatments. The gamma index offers the possibility of novel real-time interventions to promote healthy behaviors.

1. Introduction

Human behavior is the single greatest determinant of health, accounting for 40% of all cases of premature death (Schroeder, 2007). Decisions individuals make regarding smoking, drinking, substance use, nutrition, and sexual behavior play profound roles in determining quality and quantity of life. Similarly, individuals with common chronic conditions such as diabetes, hypertension, and HIV make daily decisions, in effect, about whether and when to take their medications, and these decisions in turn have important effects on health.

Healthcare providers want those with risky behaviors to abstain from engaging in those behaviors. Similarly, providers want those with chronic conditions to adhere to their medical regimens—i.e., to take their medications as prescribed, typically daily. These two actions—abstinence and adherence—may be considered as binary outcomes. Abstinence requires the individual not to engage in a specific behavior; adherence asks the individual to engage in a specific behavior. This conceptual equivalence maybe expressed mathematically as a binary function. On a daily basis, either the individual took their medication, or didn't; either the individual smoked that day, or didn't. (This is not to overlook that medication adherence is voluntary, but not compulsive, while use of an addictive substance is compulsive but not voluntary.)

Yet, in clinical trials of treatment, adherence and abstinence are measured quite differently. Medication adherence is typically measured by self-report, pill counts, or prescription data (Berg and Arnsten, 2006). Abstinence measures vary widely. For smoking, typical measures include whether the individual has smoked in the past 7 days, past 30 days, or whether a biochemical marker such as cotinine is present (Hughes et al., 2003). For drinking, self-report is typically used, perhaps

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via a 30-day timeline follow-back interview, sometimes confirmed by the biomarker ethyl glucuronide.

More significantly, these measures fail to account for the rich variation in the pattern of the behavior. These patterns of adherence or abstinence may further contribute to prognosis. Consider, for example, three individuals with HIV infection who take 90% of their prescribed doses of medication over a defined period of time. One takes the first 90% of all doses consecutively and misses the last 10%. Another misses every 10th dose. The third person misses 10% of his doses at random. Current measures would describe all three with similar levels of adherence. But their patterns of adherence are quite different and may result in differing biological outcomes such as viral load.

We have developed a novel measure of adherence and abstinence, the gamma index, which accounts for patterns of behavior. The gamma index includes information about each dose taken (or missed), can be used to model the effect of adherence and abstinence on clinically relevant biologic outcomes, and can inform real-time interventions to improve health behaviors.

The goals of this work are to (1) introduce gamma; (2) assess its ability to improve the explanatory power of interventions for alcohol misuse; and (3) suggest other applications of gamma in future research. We hypothesize that gamma will improve the modeling of the relationship between substance use behaviors and long-term abstinence rates.

Substance use and medication adherence are critical determinants of health. The leading "actual" causes of death in the United States (McGinnis and Foege, 1993) are tobacco use, poor diet and physical inactivity, and alcohol use (Mokdad, 2004). Together, these behavioral risks account for 38% of all US deaths (Mokdad, 2004). Each represents a modifiable set of behaviors in which individuals may abstain (tobacco or alcohol), engage in a healthful fashion (proper diet, adequate physical activity, or moderate drinking), or engage in an unhealthful fashion (poor diet, inactivity, or hazardous/harmful/dependent drinking). The leading causes of mortality are heart disease, cancer, and chronic lung disease (Murphy et al., 2010). These conditions are causally associated with smoking, hypertension, diabetes, and hyperlipidemia. In younger age groups and disadvantaged populations, HIV is a leading cause of death. These conditions are amenable to treatment with effective medications, for which adherence to proper dosing—insulin, oral hypoglycemics, antihypertensives, antivirals—is a critical determinant of clinical outcome (Arnsten et al., 2001; Haynes, 2008; Cramer et al., 2008).

Of note, current assessments of adherence and abstinence vary widely. Despite their behavioral and mathematical similarity, diverse measures have been used to measure adherence and abstinence (Haynes, 2008; Cramer et al., 2008). These measures employ a variety of techniques, including self-report, electronic pill counts, and biomarker assessment. Common measures of adherence and abstinence are summarized in Tables 1 and 2.

What is lacking is a unified approach to summarize these disparate measures, which, in general, measure similar phenomena. In addition, current methods used to summarize adherence and abstinence fail to account for the pattern of use (or nonuse). Current measures generally measure, in some fashion, the number of doses taken over a defined period of time divided the number of doses prescribed over that interval. We will refer to this as mean (μ) or average adherence.

Table 1
Adherence measures.

Adapted from References 9, 26, 27 (Cramer et al., 2008; DiMatteo, 2004; Osterberg and Blaschke, 2005)
Self-report
Pill counts
Pharmacy administrative data
Electronic medication cap data
Medication Possession Ratio
Collateral report
Physical test, drug level

Table 2
Measures of abstinence used in substance use trials.

Alcohol	Tobacco	Prescription/ Illicit drugs
Self-reported measures		
Drinks/week	Smoking last 7 days	Recent use
Binges/month	Smoking last 14 days	
% of subjects with no heavy drinking days	Smoking last 30 days	
Biochemical measures		
Ethylglucuronide	Exhaled carbon monoxide	Urine metabolites
Carbohydrate-deficient transferrin (Bergström and Helander, 2008; Hahn et al., 2010)	Cotinine	
Phosphatidylethanol (Wurst et al., 2012)	Sodium thiosulfate	
Apolipoprotein J (Wurst et al., 2012)		

What these measures do not address is the pattern of which days a patient adheres or abstains. This pattern may also affect clinical outcomes. We provide examples below from two conditions.

HIV. Some studies suggest a link between patterns of adherence to antiretroviral therapy and virologic outcome. Parienti et al. found that for HIV+ subjects on protease inhibitors, the proportion of doses taken (i.e. mean adherence) was a better predictor of change in viral load than the duration of consecutively missed doses (Parienti et al., 2010). In contrast, the same group found that consecutively missed doses (i.e. the pattern of adherence) was a better predictor of outcome for subjects on nonnucleoside reverse transcriptase inhibitors (Parienti et al., 2008). Gras et al. found that longer periods of treatment interruption and average adherence were independently associated with virologic outcome in 81 HIV+ individuals taking raltegravir (Gras et al., 2012).

Alcohol. Studies of patterns of drinking have largely focused on intermittent heavy drinking or bingeing, a risk behavior for numerous other conditions. Less attention has been paid to quantification of daily drinking patterns over an extended period of time, or patterns of abstinence in drinkers during treatment. One systematic review found that binge drinkers were at increased risk of injury and coronary artery disease than non-binge drinkers. (Rehm et al., 2003).

Network analysis offers a means to assess the pattern of adherence (or abstinence). In this paper, we propose a novel measure of connectedness that conceptualizes adherence and abstinence as networks that exist as a linear graph, in a single dimension, that of time.

2. Conceptual model: Abstinence and adherence modeled as networks of connectivity

Network analysis allows interactions among members of a group to be modeled with graphs. Common network models may examine objects that exist in two dimensions, like a street grid, or in a dimensionless space, such as social networks (Christakis and Fowler, 2007). Nodes, or vertices, represent members of the network and edges the relationships between the members. Graph theory is then used to study the network.

Using these concepts, the behavior of adherence can be expressed as a linear graph, which can be thought to lie along an axis of time. Here, the nodes correspond (in order) to the scheduled doses of a drug regimen, with each node labeled "adherent" or "non-adherent." Edges are then drawn, connecting either two consecutive adherent nodes, or two consecutive non-adherent nodes. So the gamma index, which positively weights the adherence-connected components and negatively weights the non-adherent-connected components, gives a measure of

connectivity of such a labeled linear graph.

We can model this linear network of behavior by measuring the strength of the connectedness of adjacent doses taken and adjacent doses missed. The algebraic derivation of gamma, shown below, is provided in the Appendix.

We note that γ would equal 1 for a patient who took all medication doses as prescribed, and 0 for a patient who skipped all doses of medication. This may have greater intuitive appeal and utility than A2.

2.1. Examples of gamma's range

Consider an individual who takes 90% of medications as prescribed. If there are 10 total doses to be taken, there are 10!/9!1! = 10 possible arrangements of medication dosing. These arrangements, and their associated indices, are given in Table 3. The index ranges between 0.7 and 0.9, with a median of 0.76, suggesting substantial variation in the pattern of adherence, even for mean adherence as good as 90%.

We can represent the variation in the values of gamma graphically. Fig. 1 displays box-and-whiskers plots of the range of values of gamma for each decile of mean adherence (0%, 10%, 20%, etc.) in a 10-dose trial. The numbers of permutations for each decile, from 0% to 100%, are, respectively, 1, 10, 45, 120, 210, 252, 210, 120, 45, 10, and 1. As shown, gamma's range is wider at the non-zero extremes of adherence (or abstinence).

Now consider the variation in adherence for an individual who again takes 90% of her medication, this time for a 20-dose regimen. Now there are 20!/18!2! = 190 potential arrangements of adherence. In this example, gamma varies from 0.6325 to 0.9025, with a median of 0.7.

Our goal is to determine whether this variation, as measured from already completed human trials of abstinence and adherence, correlates with variation in clinically meaningful outcomes.

2.2. Distribution of gamma

We have written a macro in SAS that can calculate the index. The code for this macro is provided in the Appendix. Fig. 2 illustrates how gamma varies based on number of prescribed doses and mean adherence. The curves show the mean values of γ for deciles of adherence with all permutations for 10, 20, 30, and 40 doses of medication. For example, an individual who takes 80% of 10 doses has 45 permutations possible. The mean value of the transformed index for all permutations at this level of adherence is 0.67. An individual who takes 80% of a 15-dose course of treatment has 455 possible permutations. The mean value of the index for these 45 permutations is 0.635. In general, as the number of assessments of adherence or abstinence increases, the mean value of gamma for any given level of adherence increases for adherence < 0.5, and decreases for adherence > 0.5. Note that, irrespective of sample size, the mean value of gamma, for all permutations, is always fixed at 0 for perfect non-adherence, 1 for perfect adherence, and by symmetry, 0.5 for 50% adherence.

The sigmoidal curves in Fig. 5 illustrate the relationship between γ and μ, at varying levels of μ, as the number of required doses increases. As the number of doses increases, the slope of the central portion of the gamma-adherence curve decreases, indicating a weaker relationship between γ and μ, so both would want to be taken into account by a clinician.

Table 3
Permutations and gamma values for a 10-dose trial with 90% adherence.

Dose 1	2	3	4	5	6	7	8	9	10	Index
1	1	1	1	1	1	1	1	1	0	0.9
1	1	1	1	1	1	1	1	0	1	0.82
1	1	1	1	1	1	1	0	1	1	0.76
1	1	1	1	1	1	0	1	1	1	0.72
1	1	1	1	1	0	1	1	1	1	0.7
1	1	1	1	0	1	1	1	1	1	0.7
1	1	1	0	1	1	1	1	1	1	0.72
1	1	0	1	1	1	1	1	1	1	0.76
1	0	1	1	1	1	1	1	1	1	0.82
0	1	1	1	1	1	1	1	1	1	0.9

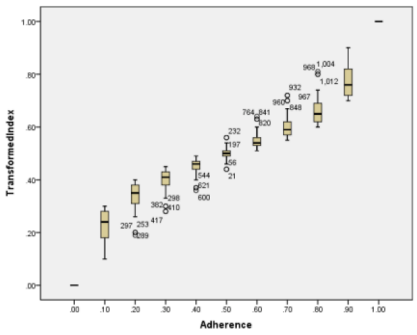

Fig. 1. Box-and-whiskers plots of gamma index range, by decile of adherence, for 10-dose trial.

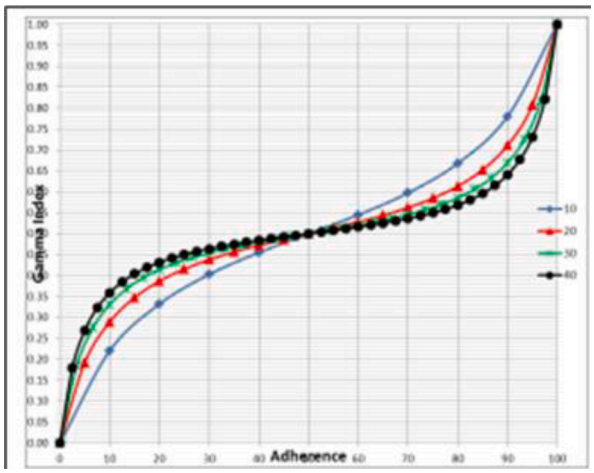

Fig. 2. The effects of total numbers of doses and adherence on gamma.

Fig. 3 illustrates the 45 permutations of adherence for an individual who takes 8 doses of medication out of the 10 prescribed (80% adherence). Note that gamma is maximal when the string of consecutive doses taken is maximal, and the missed doses are at the beginning and end of treatment.

Inspection of Figs. 3–6 reveals some properties of gamma that suggest testable hypotheses:

In Fig. 4, there is more variation in the value of gamma at the extremes of adherence. This suggests that gamma-dependent clinical endpoints may show a wider range at the extremes of adherence (or abstinence).

Also from Fig. 1, it is apparent that certain permutations of a fixed level of mean adherence yield a gamma index higher than that of other permutations at a higher level of mean adherence.

Fig. 2 shows that changes in gamma (i.e. slopes) are steepest at the extremes of mean adherence, suggesting that interventions to improve adherence might have their greatest effect on gamma-dependent outcomes in individuals already quite adherent (or quite non-adherent).

From Fig. 2, the slope of the gamma curve becomes steeper at the extremes as the number of doses (or abstinent intervals) increases.

Fig. 3 suggests that if adherence is < 100%, γ may be maximized by missing doses in brief strings of similar size at the beginning and end of treatment. Whether this would optimize clinical outcome for suboptimal adherence is unknown.

In this paper, we offer a re-analysis using gamma of data from a

10-dose course, 80% adherence, all permutations.
1=dose taken; 0=dose missed.

Index	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
0.81	0	1	1	1	1	1	1	1	1	0
0.8	1	1	1	1	1	1	1	1	0	0
0.8	0	0	1	1	1	1	1	1	1	1
0.74	1	1	1	1	1	1	1	0	1	0
0.74	1	0	1	1	1	1	1	1	1	0
0.74	0	1	1	1	1	1	1	1	0	1
0.74	0	1	0	1	1	1	1	1	1	1
0.73	1	1	1	1	1	1	1	0	0	1
0.73	1	0	0	1	1	1	1	1	1	1
0.69	1	1	1	1	1	1	0	1	1	0
0.69	1	1	0	1	1	1	1	1	1	0
0.69	0	1	1	1	1	1	1	0	1	1
0.69	0	1	1	0	1	1	1	1	1	1
0.68	1	1	1	1	1	1	0	1	0	1
0.68	1	1	1	1	1	1	0	0	1	1
0.68	1	1	0	0	1	1	1	1	1	1
0.68	1	0	1	1	1	1	1	1	0	1
0.68	1	0	1	0	1	1	1	1	1	1
0.66	1	1	1	1	1	0	1	1	1	0
0.66	1	1	1	0	1	1	1	1	1	0
0.66	0	1	1	1	1	1	0	1	1	1
0.66	0	1	1	1	0	1	1	1	1	1
0.65	1	1	1	1	1	0	0	1	1	1
0.65	1	1	1	1	0	1	1	1	1	0
0.65	1	1	1	0	0	1	1	1	1	1
0.65	0	1	1	1	1	0	1	1	1	1
0.64	1	1	1	1	1	0	1	1	0	1
0.64	1	1	1	1	1	0	1	0	1	1
0.64	1	1	1	1	0	0	1	1	1	1
0.64	1	1	0	1	1	1	1	1	0	1
0.64	1	1	0	1	0	1	1	1	1	1
0.64	1	0	1	1	1	1	1	0	1	1
0.64	1	0	1	1	0	1	1	1	1	1
0.62	1	1	1	1	0	1	1	1	0	1
0.62	1	1	1	1	0	1	0	1	1	1
0.62	1	1	1	0	1	1	1	1	0	1
0.62	1	1	1	0	1	0	1	1	1	1
0.62	1	0	1	1	1	1	0	1	1	1
0.62	1	0	1	1	1	0	1	1	1	1
0.61	1	1	1	1	0	1	1	0	1	1
0.61	1	1	0	1	1	1	1	0	1	1
0.61	1	1	0	1	1	0	1	1	1	1
0.6	1	1	1	0	1	1	1	0	1	1
0.6	1	1	1	0	1	1	0	1	1	1
0.6	1	1	0	1	1	1	0	1	1	1

Fig. 3. 10-dose course, 80% adherence, all permutations. 1 = dose taken; 0 = dose missed.

completed clinical trial of treatment for alcohol misuse. We are also re-examining datasets from completed clinical trials in three other domains: (1) adherence to Highly Active Antiretroviral Therapy (HAART) in subjects with HIV/AIDS; (2) adherence to buprenorphine/naloxone and abstinence from opiates in trials of opioid dependence treatment; and (3) abstinence from tobacco in two trials of smoking cessation.

3. Methods

3.1. Example using data from completed trials

As an illustrative case, we present data from a published trial of a brief intervention for individuals with alcohol use disorders visiting a hospital emergency department (ED) (D'Onofrio et al., 2008, 2012). All analyses were performed with SAS v9.4 (SAS Institute, Cary, NC). The study was approved by the Human Investigation Committee of Yale University.

In the study, D'Onofrio et al. randomized 494 adults with hazardous or harmful drinking to receive either a brief negotiation interview (BNI) or scripted discharge instructions addressing the harms of drinking, delivered both verbally and on paper (D'Onofrio et al., 2008). Primary endpoints were drinks per week and number of binge days in past month both assessed by self-report at 6 and 12 month time points.

At 12 months, there was no difference in drinking outcomes between groups. Among motivational interview subjects, the mean number of drinks per week at 12 months was 3.8 less than the 13.6 reported at baseline. Among discharge instructions participants, drinks per week decreased by 2.6 from 12.4 at baseline. Similarly, binges per month decreased by 2.0 from a baseline of 6.0 in the motivational interview group, and 1.5 from 5.4 among discharge instructions participants.

3.2. Analysis of gamma as an additional abstinence outcome

We evaluated gamma as a marker of abstinence pattern in trial assessing the impact of intervention on alcohol use. The primary objective of these analyses is to demonstrate that the interventions result in differences in the gamma index. Abstinence gamma indices were computed from the 30-day self-reported recall for drinks per week and bingeing separately. For drinks per week, abstinence was defined as the absence of any drinking during a day and coded as "0″. For binge days, abstinence was defined as the absence of any binge episodes for a particular day and coded as "0". Lower gamma index corresponded to lower drinking days or binge episodes. Likelihood-based ignorable analysis using a mixed model was used to compare the gamma index between groups (Dmitrienko et al., 2005; Molenberghs, 2004). These models included fixed effects for the intervention, time and their interaction. Baseline gamma index was also included as a covariate. Linear contrasts were used to estimate intervention group differences and 95% confidence intervals at each individual follow-up time. To describe the utility of gamma as an outcome, we determined standardized treatment effect sizes (i.e. difference in outcome means divided by the standard deviation of the outcome) for gamma as well as the primary endpoints of the alcohol study. In addition, to examine the utility of gamma above and beyond typical summaries of abstinence we also evaluated the use of both gamma index and the proportion of abstinence days as dependent variables in a multivariate mixed model analysis, and use gamma index as dependent variable with covariate adjustment for weekly drinks. We considered changes in effect sizes to examine whether gamma might yield additional insights into clinical trial results not otherwise apparent with the use of conventional measures of changes in drinking.

4. Results

Tables 4 and 5 show the results of the mixed model analysis. Table 4 displays the results for changes in number of drinks consumed per week; Table 5 shows changes in binge days of drinking.

In the mixed model analysis in Table 4, the standardized effect sizes of changes in drinks per week at both 6 months and 12 months were close to zero, and were not statistically significant. However, the effect sizes of the gamma index derived from drinks per day (i.e. abstinence from any drinks in a day assessed over past 30 days) was −0.15 for 6 month and 12 month overall ($p = 0.05$), meaning participants in the BNI

Table 4
Reanalysis of alcohol study.

	Weekly Drinks	Gamma index	Proportion of days abstinent
6 months difference (BNI – DI)			
Effect (95% CI)	0.40 (−2.03, 2.83)	−0.04 (−0.08, 0.003)	0.02 (−0.02, 0.07)
Standardized Effect size	0.03 (−0.15, 0.21)	−0.17 (−0.35, 0.01)	0.11 (−0.09, 0.31)
P value	0.75	0.07	0.26
12 months difference (BNI – DI)			
Effect (95% CI)	0.12 (−2.20, 2.44)	−0.03 (−0.08, 0.01)	0.04 (−0.003, 0.08)
Standardized Effect size	0.01 (−0.17, 0.19)	−0.14 (−0.32, 0.05)	0.19 (−0.01, 0.38)
P value	0.92	0.15	0.07
6 and 12 months overall difference (BNI – DI)			
Effect (95% CI)	0.26 (−1.81, 2.33)	−0.04 (−0.07, 0)	0.03 (−0.004, 0.07)
Standardized Effect size	0.02 (−0.14, 0.18)	−0.15 (−0.30, 0)	0.15 (−0.02, 0.32)
P value	0.81	**0.05**	0.08

	Gamma index with weekly drinks as covariate	Bivariate mixed model analysis	
		Gamma index	Proportion of days abstinent
6 months difference (BNI – DI)			
Effect (95% CI)	−0.04 (−0.08, −0.01)	−0.04 (−0.08, 0.001)	0.04 (0.004, 0.09)
Standardized Effect size	−0.18 (−0.34, −0.03)	−0.17 (−0.34, 0.01)	0.20 (−0.02, 0.42)
P value	0.02	0.06	0.07
12 months difference (BNI – DI			
Effect (95% CI)	−0.03 (−0.07, 0.001)	−0.03 (−0.08, 0.008)	0.05 (−0.004, 0.10)
Standardized Effect size	−0.14 (−0.28, 0.01)	−0.13 (−0.30, 0.03)	0.22 (−0.02, 0.45)
P value	0.06	0.12	0.07
6 and 12 months overall difference (BNI – DI)			
Effect (95% CI)	−0.04 (−0.07, −0.01)	−0.04 (−0.07, −0.001)	0.05 (0.004, 0.10)
Standardized Effect size	−0.16 (−0.28, −0.04)	−0.15 (−0.30, −0.01)	0.21 (0.02, 0.40)
P value	**0.01**	0.04	0.03

	Binge days	Gamma index
6 months difference (BNI – DI)		
Effect (95% CI)	−0.1 (−1.2, 1.01)	−0.01 (−0.04, 0.03)
Standardized Effect size	−0.01 (−0.20, 0.17)	−0.02 (−0.20, 0.15)
P value	0.87	0.80
12 months difference (BNI – DI)		
Effect (95% CI)	0.14 (−1.04, 1.31)	−0.01 (−0.05, 0.03)
Standardized Effect size	0.02 (−0.16, 0.20)	−0.05 (−0.22, 0.13)
P value	0.82	0.59
6 and 12 months overall difference (BNI – DI)		
Effect (95% CI)	0.03 (−0.94, 1.00)	−0.01 (−0.04, 0.03)
Standardized Effect size	0.004 (−0.15, 0.16)	−0.04 (−0.19, 0.12)
P value	0.96	0.64

*Drinks per week and gamma index (smaller values correspond to longer strings of abstinence) or proportion of abstinent days as outcome variables in the mixed model analysis.
* Binge days and gamma index (smaller values indicate longer strings of days of non-binge drinking) alone as outcome variable in mixed model analysis.

Table 5
Reanalysis of alcohol study: Binge days and gamma index (smaller values indicate longer strings of days of non-binge drinking) alone as outcome variable in mixed model analysis.

	Binge days	Gamma index
6 months difference (BNI – DI)		
Effect (95% CI)	−0.1 (−1.2, 1.01)	−0.01 (−0.04, 0.03)
Standardized Effect size	−0.01 (−0.20, 0.17)	−0.02 (−0.20, 0.15)
P value	0.87	0.80
12 months difference (BNI – DI)		
Effect (95% CI)	0.14 (−1.04, 1.31)	−0.01 (−0.05, 0.03)
Standardized Effect size	0.02 (−0.16, 0.20)	−0.05 (−0.22, 0.13)
P value	0.82	0.59
6 and 12 months overall difference (BNI – DI)		
Effect (95% CI)	0.03 (−0.94, 1.00)	−0.01 (−0.04, 0.03)
Standardized Effect size	0.004 (−0.15, 0.16)	−0.04 (−0.19, 0.12)
P value	0.96	0.64

arm showed lengthier strings of abstinence from drinking. When the model was controlled with drinks per week, the effect size increased to −0.16, with p = 0.01. These results indicated that gamma was able to demonstrate an intervention effect, when conventional measures of changes in drinking could not. In addition, when gamma was modelled as an outcome, simultaneously with the conventional outcome of proportion of abstinent days, in a bivariate mixed model analysis, both outcomes attained a lower P value, indicating a stronger statistical association (Table 4).

Table 5 shows the results of binge days and gamma derived from binge days. Both outcomes had small effect sizes and were statistically insignificant. Gamma did not provide additional insights into any potential effect of the intervention on patterns of binge drinking.

5. Discussion

We have introduced a new index to measure the connectedness of any human health behavior, and to show that this measure, gamma, may yield additional insights into patterns of behavior. The gamma index uses information regarding the daily presence, or absence, of a behavior of interest, over a defined period of time. The index ranges between 0 and 1, where 0 indicates complete absence of the behavior, and 1 indicates presence of the behavior daily. Gamma is akin to a second moment for the proportion of days exhibiting the behavior, similar to the variance of a random variable. In this manuscript, we focus on abstinence to alcohol; in subsequent work we will provide examples of gamma's use in modeling adherence to medication.

In the 2008 D'Onofrio study, which showed no changes in drinks per week or binge days between intervention and controls (although both groups drank less over time), gamma found differences in drinking patterns. Specifically, at 6 and 12 months, intervention participants had a lower gamma score than controls for changes in drinks per week, indicating, again, that their drinking became more sporadic than that of controls.

Modeling gamma as a covariate or outcome variable in studies of substance misuse may yield insights into the connectedness or the behavior as treatment progresses. It serves as an additional measure of behavior, in addition to more conventional measures of alcohol use, substance use, or smoking. Gamma provides additional insights into traditional measures of treatment adherence or fidelity, and provides a unified approach to resolving the disparate measures used in studying adherence and abstinence.

In the case of diseases like HIV or diabetes, gamma may be modeled as an independent variable to assess the impact of treatment adherence interventions on clinically pertinent intermediate endpoints, like changes in viral load or glycated hemoglobin.

The gamma index has several potential applications. Gamma may be used to model any desired behavior, whether a healthful one (taking medicine, exercising, wearing sunscreen), or a risky one (smoking, drinking, using illicit drugs.) It may offer insights into ways to maximize clinical outcomes, by facilitating the design of interventions tailored to individual patients' patterns of substance use or medication/treatment regimen adherence. The growing availability of big-data technologies such as wearable sensors will facilitate collecting the data needed to calculate gamma. In resource-poor environments, identifying ways to optimize the values of gamma may yield insights on more equitable ways to distribute scarce medications within a population. More widespread use of gamma may facilitate the science and practice of precision medicine (Collins and H., 2015).

There are some limitations in the uses of the gamma index. It is possible that different conditions, diseases, and behaviors may have different ranges of "optimal" gamma values that maximize clinical benefit. This needs to be explored in future work. Patterns of adherence or abstinence that yield higher values of gamma should not be assumed to lead to improved clinical outcomes. Second, whether the index will have greater utility as a correlate of clinical outcome or as an additional descriptive metric of health behavior needs to be explored further. Again, this may depend on the condition being studied. Finally, certain health behaviors are not easily dichotomized, and how to modify gamma to characterize these behaviors needs further exploration. For example, individuals may take their medications daily, but with irregular timing intervals or suboptimal dosing. Other novel methods are being developed that suggest a link between medication timing and clinical outcomes (Huvanandana et al., 2022).

6. Conclusions

The gamma index offers a new way to model human health behavior. Mathematically, it represents a measure of connectivity for nodes in a linear graph. By offering a quantitative measure of the pattern of health behaviors, such as adherence and abstinence, it can be used as an additional measure to supplement traditional measures of adherence to medication, and abstinence from addictive substances. Results from reanalysis of data from a study of behavioral treatment for alcohol use disorders demonstrates gamma's promise as a measure that can offer new insights into the effects of interventions on addictive behaviors. Additional studies of gamma, now in progress, may offer additional insights.

7. Ethics approval and consent to participate

The data re-analyzed in this study were drawn from trials approved by the Human Investigation Committee of Yale University.

8. Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

9. Consent for publication

Not applicable.

CRediT authorship contribution statement

Steven L. Bernstein: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft. **Fangyong Li:** Data curation, Formal analysis, Software, Writing – review & editing. **Fuad Abujarad:** Formal analysis, Methodology, Writing – review & editing. **David R. Grant:** Conceptualization, Methodology, Writing – review & editing. **Gail D'Onofrio:** Funding acquisition, Resources, Writing – review & editing. **James Dziura:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A

Derivation of gamma

Consider a behavior that needs to be repeated N times. The behavior may refer to daily adherence (like pill-taking) or to abstinence (like avoiding harmful substances). The timing interval may vary—daily would be typical in clinical trials, but other intervals are possible (for example, a drug that needs to be taken twice daily).

For the derivation of gamma, we will refer to adherence to medication, but recognize that any behavior that can be modeled as a binary sequence may be substituted.

If the patient is required to take n doses of medication, but takes p of them, and misses x doses, then

$$p + x = n \tag{1}$$

Now, let pi equal the count of consecutively taken doses of medication in the ith string of m sets of consecutively taken doses, and xk equal the count of consecutively missed doses of medication in the kth string of n sets of consecutively missed doses.

And N = number of prescribed doses.

What we seek is a measure that positively counts periods of adherence, and negatively counts periods of non-adherence, weighted over the duration of study. A first attempt at this might be

$$A1 = (\sum_{i=1}^{m} pi - \sum_{k=1}^{n} xk)/N \tag{2}$$

but since

$$(\sum_{i=1}^{m} pi + \sum_{k=1}^{n} xk) = 1 \tag{3}$$

we see that that A1 + 1 is just twice mean adherence μ, so as we've noted, ignores the pattern of adherence. To remedy this, we now introduce the index

$$A2 = (\sum_{i=1}^{m} pi^2 - \sum_{k=1}^{n} xk^2)/N^2 \tag{4}$$

to measure adherence (or abstinence). Akin to variance, this is in some sense a second moment of the binary sequence describing daily adherence weighted over the interval of duration, and as such, measures the spread of overall adherence. Along with mean adherence μ, it gives a more complete description of the pattern of adherence than just μ alone.

Range of the index and its normalization γ

If a patient takes all n doses of medication as prescribed, the value of the index in (2) is $n^2/n^2 = 1$. If a patient misses every dose, the value of this index is $-(n^2/n^2) = -1$. Thus, the range of the index is [−1, 1].

The index may be made more intuitively meaningful to a clinician if it ranges from 0 to 1. So just as μ = (A1 + 1)/2, we now set

$$\gamma = (A2 + 1)/2, \tag{5}$$

that is

$$\left(\left[\left(\sum_{i=1}^{m} pi^2 - \sum_{k=1}^{n} xk^2\right) \Big/ N^2\right] + 1\right) \Big/ 2 \tag{6}$$

Where N = number of doses to be taken

p_i = the count of consecutively taken doses of medication in the ith string of m sets of consecutively taken doses

xk = the count of consecutively missed doses of medication in the kth string of n sets of consecutively missed doses

Note that γ would equal 1 for a patient who took all medication doses as prescribed, and 0 for a patient who skipped all doses of medication. This may have greater intuitive appeal and utility than A2.

Using gamma: examples

From the binomial expansion, if there are n potential doses of a drug to be taken, and the patient takes p of them, then there are

$$\binom{n}{p} = \frac{n!}{p!(n-p)!} \tag{7}$$

potential arrangements of doses. So, for example, if the patient takes 8 out of 10 prescribed doses of a medication, there are (10!)/(8!)(2!) = 45 potential arrangements of the 8 doses in a 10-dose timeframe. Appendix Fig. 3 shows three such arrangements, where the overall adherence is 80%. In each, a green ball indicates a dose taken; a red ball indicates a skipped dose.

Thus, the index allows us to develop an ordinal ranking of the adherence patterns of all subjects, even though each took 80% of the prescribed doses. Longer strings of adherence (i.e. taking the medicine) raise the index; longer strings of non-adherence lower the index. Gamma can be modeled as a continuous variable, although there is no discrete quantitative relationship between values. A gamma of 0.8 is not "twice as good" as an index of 0.4. A higher index simply denotes greater connectivity among the doses of medication taken.

One may hypothesize that, for any given mean adherence, the pattern that maximizes γ will result in the optimum clinical outcome. In the case of adherence to antiviral therapy for HIV infection, that outcome could be viral load. For a diabetic, it could be glycated hemoglobin. Many other examples from clinical medicine could be developed. If used to supplement μ as a measure of abstinence from use or abuse of substances such as alcohol, tobacco, or illicit substances, γ could provide a more "granular" measure of the efficacy of the intervention. And, as noted earlier, HIV researchers have noted that longer stretches of non-adherence are associated with poorer virologic response (Genberg et al., 2012).

Supplemental Figure provides the SAS macro used to calculate the gamma index.

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102172.

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