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Analyzing feed-forward loop relationship in aging phenotypes: Physical activity and physical performance

Arindam RoyChoudhury[a,*], Thuy-Tien L. Dam[b], Ravi Varadhan[c], Qian-Li Xue[c,d,e], Linda P. Fried[f,g]

[a] Department of Biostatistics, Columbia University, New York, NY, USA
[b] Division of Geriatric Medicine and Aging, Department of Medicine, Columbia University, New York, NY, USA
[c] Division of Geriatric Medicine and Gerontology, Center of Aging and Health, Department of Medicine, Johns Hopkins University, USA
[d] Department of Biostatistics, Johns Hopkins University, USA
[e] Department of Epidemiology, Johns Hopkins University, USA
[f] Department of Epidemiology, Columbia University, USA
[g] Department of Medicine, Columbia University, USA

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ABSTRACT

We present evidence of feed-forward loop relationships and positive association between physical activity and performance levels, which are components of frailty, using measures from 431 high functioning women initially aged 70–79 years followed over 7 visits. Physical activity levels were assessed using a questionnaire. Grip strength was measured using a handheld dynamometer and usual walking speed was measured over 4-m. The results suggest that a reduction in physical activity would not only degrade physical performance, but it would further reduce physical activity through declines in physical performance. As both physical activity and physical performance impact frailty, improvement of physical activity could help reduce frailty directly as well as indirectly via improved physical performance. Our findings support a priori hypothesis that feed-forward loops are present in the phenotype of frailty, which is due to dysregulated energetics. A methodologically broader implication is that we introduce modeling and analysis of feed-forward loop data here. The feed-forward loop, as we define it, is different from the concept of feedback loops used in biochemical systems. Generalizing our model of two-variable feed-forward loop, three, four or multivariable feed-forward loop can be applied to other biological systems.

1. Introduction

Frailty is a clinical syndrome identifying a subset of older adults at increased risk for adverse outcomes (Fried et al., 2001; Bandeen-Roche et al., 2006; Walston et al., 2006). It is formally defined based on 3 of five criteria being present: shrinking, weakness, poor endurance, slowness and physical inactivity (Fried et al., 2001; Bandeen-Roche et al., 2006). Evidence suggests the hypothesis that the vulnerability to adverse outcomes associated with the frailty results from dysregulation of physiologic systems in a complex multidirectional relationship (Fried et al., 2001; Cohen et al., 2013; Fried et al., 2009). Dynapenia and physical inactivity, which are the initial components (Xue et al., 2012) of the frailty syndrome, have been associated with each other as well as with phenotypic variables from other systems. In particular, dynapenia has been associated with decline in walking speed (Rantanen et al., 1998), major mobility disability (Marsh et al., 2011), and decline in physical activity (Ferrucci et al., 2002), which has itself been associated with decline in physical functioning (Brach et al., 2003). These declines have been associated with increased mortality through meta-analyses or otherwise (Cooper et al., 2014; Klepin et al., 2010). In particular, decline in walking speed has been shown to be a predictor of survival in older adults (Studenski et al., 2011). These observations point to an important next question: "Is frailty the manifestation of faulty intercommunication between inadequately functioning biological systems, resulting in loss of resilience to stressors?" If the dynamics of dysregulation underlying the frailty syndrome are empirically established, then frailty could potentially be both prevented and treated, and

* Corresponding author at: 722 W 168th Street, 6th Floor, New York, NY 10032, USA. Tel.: +1 212 342 1268; fax: +1 212 305 9408.
E-mail address: ar2946@columbia.edu (A. RoyChoudhury).

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possibly reversed, by improving the functionality of the complex dynamical systems.

A special case of multisystem models is the feed-forward loop. The feed-forward loop is a cyclical structure of influence. Formally, we define it as a phenomenon where a variable influences its own future values through other variable(s) (irrespective of whether it directly influences its future value or not). In other words, a feed-forward loop is said to exist if a variable indirectly influences itself through other variable(s), irrespective of any direct influence (Fig. 1). For example, physical activity level can potentially influence future physical activity level through influencing physical performance, which can then influence future physical activity. *(Note that, the feed-forward loop, as we define it, is different from the concept of feedback loops used in biochemical systems.)* A feed-forward loop is a basic component of a complex systems model, and therefore testing for feed-forward loop is a first step towards figuring out the complex structure of a system.

By studying feed-forward loops, we could provide insight into how multiple systems jointly affect each other and contribute to development of frailty as a dynamical system. In particular, reductions in physical activity or physical performance could have a snowballing effect on overall health. For example, if there is a feed-forward loop between physical activity and physical performance, then a reduction in physical activity would not only degrade physical performance, but it could further reduce physical activity as a result of diminished physical performance. Thus, it would be concluded that the components of a dynamical system associate as a complex loop structure. (i.e. they are associated through at least two separate relations with the roles of predictors and outcome switched in these two relations) (e.g. $X \rightarrow Y$ and $Y \rightarrow X$; in the former X and Y are predictors and outcomes respectively; in the latter their roles are switched: see Figs. 1 and 3; see details in Section 2.7). Moreover, as these two variables are components of frailty, it would also provide evidence that the development of frailty involves dynamical systems. If one of the components is improved then it would have a strong effect on all components and subsequently it would potentially have a strong effect on frailty. Varadhan et al. (2008) have argued that analysis of examples of the complex dynamical system presumed to underlie frailty is the critical next step for the science of frailty. It is, therefore, of interest to ask if there is a feed-forward loop present in the system that regulates the relationship between physical activity and physical performance. However to our knowledge, no one has addressed the feed-forward loop structure between physical activity and muscle strength or physical performance using cross-sectional or longitudinal designs.

A key limitation to the testing for the multidirectional loop-structured system is the lack of statistical models that are finely tuned to analyze interacting biological systems with looping structures. To address this lack, the objective of this paper is to utilize novel statistical feed-forward loop methods to test for evidence of intercommunication between physical activity and performance levels (grip strength, walking speed) among 431 women aged 70–79 who participated in the Women's Health and Aging Study II (WHAS II; Fried et al., 2000) and had walking speed, grip strength, or physical activity measures over seven visits (Xue et al., 2012). We hypothesize that physical activity increases muscle strength and performance, both boost fitness level, on which thereby improves physical performance level and further heightens physical activity. This hypothesis implies that physical activity and performance level do not affect frailty simply in a linear uni-directional manner, rather the relationship has a complex loop. If one of the components is improved then it would have a strong effect on all components, which will also have a strong effect on frailty.

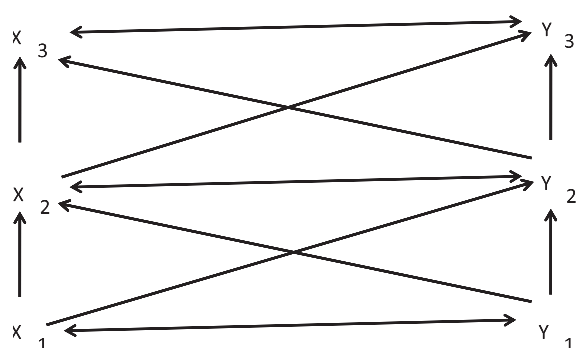

Fig. 1. Feed-forward loop between *X* and *Y*.

2. Materials and methods

2.1. Overview of statistical approach

Several approaches to analyze multisystem dysregulation in older adults have been examined previously. First, a general framework for multisystem dysregulation analyses using dynamical systems modeling for physiological system changes over short time interval have been done before (Varadhan et al., 2008). However, this method was not specifically designed for feed-forward loop analyses; rather it was a general framework to be implemented to suit specific cases. Second, Cohen et al. (2013) introduced a distance based approach for predicting and detecting multisystem dysregulation. However, their method is based on summary statistics instead of likelihood-based methods; therefore, this method has less power and does not achieve full statistical efficiency.

To address the lack of proper modeling and estimation in multisystem dysregulation in older adults, we propose new approaches to analyze and test for feed-forward loop, and apply them in the WHAS II. We model the relationship as a two-sided Granger-causality model (also known as cross-lagged panel model) (Nelson and Schwert, 1982; Granger, 1969). It is defined for two time series $\{X_t\}$ and $\{Y_t\}$ such that (1) past values of X are associated with Y after adjusting for the past values of Y, and (2) past values of Y are associated with X after adjusting for the past values of X (Fig. 1). The feed-forward loop relationship thus defined can be analyzed as a bivariate time-series (or cross-lagged panel model) or otherwise (Campbell, 1963; Kenny, 1975).

2.2. Participants

The Women's Health and Aging Study II is a prospective population-based cohort study of 436 women initially aged 70–79 years who were representative of the two-thirds highest functioning women living in the community. Study eligibility criteria were: (a) either no difficulty or difficulty in only one of the following tasks: mobility, upper extremity, household management tasks, and self-care tasks; and (b) Mini-Mental State Examination score of 24 or greater. Participant characteristics and recruitment information were reported elsewhere (Xue et al., 2012). Interviews and physical examinations were conducted at baseline and at 6 follow-up visits (approximately 18 months apart except for the interval between the third and the fourth visit, which was, on average, 3 years), for a median follow-up of 12 years (between 1994 and 2009). The analytic sample consisted of 431 women for whom we had data on self-reported physical activity levels at baseline. In longitudinal analyses, 95% and 67% of the 431 women contributed 2 or more and 5 or more longitudinal measurements of physical activity, respectively, before study dropout or death. The study was approved by the Johns Hopkins University Institutional Review Board.

2.3. Measures of physical activity

Physical activity level was assessed using a shortened version of the Minnesota Leisure Time Activities Questionnaire (Pereira et al., 1997), which includes 4 exercise activities (walking for exercise, dancing, bowling and strengthening activities) and 2 lifestyle activities (strenuous household and outdoor activities e.g. scrubbing, gardening). Level of participation in each activity was assessed by self-reported frequency and duration of participation during the past 2 weeks and converted into kcal unit of energy spent into lifestyle activities and exercise.

2.4. Measures of performance levels

Performance levels were assessed as grip strength and walking speed. Grip strength was measured using a JAMAR hand dynamometer (Model #BK-7498; Fred Sammons Inc., Burr Ridge, Illinois). Testing was done with the participant in a seated position and the elbow flexed at 90°. Three measurements were taken for each hand and the maximum measurement (kg), regardless of handedness, was used in these analyses. Walking speed was calculated based on the time to complete