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Analyzing Feed-Forward Loop Relationship in Aging Phenotypes: Physical Activity and Physical Performance

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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-meters. 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.

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Introduction

Frailty is a clinical syndrome identifying a subset of older adults at increased risk for adverse outcomes.^{4,17,18} It is formally defined based on 3 of five criteria being present: shrinking, weakness, poor endurance, slowness and physical inactivity.^{4,17} 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^{4,5,16} Dynapenia and physical inactivity, which are the initial components¹⁰ 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 speed¹, major mobility disability¹⁴, and decline in physical activity⁷, which has itself been associated with decline in physical functioning.⁸ These declines have been associated with increased mortality through meta-analyses or otherwise^{20,21}. In particular, decline in walking speed has been shown to be a predictor of survival in older adults⁶. 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 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 toward 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 “Statistical Approaches” Section.) 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.⁹ 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 II³) and had walking speed, grip strength, or physical activity measures over seven visits¹⁰. 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.

Materials and Methods

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 before⁹. 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.⁵ 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)^{11,2}. 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^{12,13}.

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 elsewhere¹⁰. 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.

Measures of physical activity

Physical activity level was assessed using a shortened version of the Minnesota Leisure Time Activities Questionnaire¹⁵, 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.

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 a 4-meter course at usual pace (m/s). Participants started from the standing position for each trial; two trials were done and the faster walking speed was used in these analyses.

Other measurements

Baseline medical histories of coronary artery disease, COPD, diabetes, osteoporosis and cancer were recorded using a questionnaire. In addition, body mass index (BMI) was measured from baseline height and weight.

Frailty Syndrome Criteria

Frailty was measured as described by Fried and colleagues^{4,17}. Five criteria were used: shrinking (BMI <18.5 kg/m² or 5% annual weight loss), weakness (low grip strength), poor endurance (exhaustion), slowness (low walking speed), and physical inactivity (low level of physical activity). Those with three or more criteria were categorized as frail, 1–2 were

categorized as prefrail, and none were nonfrail. These criteria were assessed at every visit. As our targeted measures (physical activity and walking speed) are used in defining frailty syndrome criteria, we did not use frailty syndrome criteria as a variable in our analyses due to the risk of confounding and high dependence between independent variables. However, frailty status was used to describe the study population.

Statistical Approaches

The series $\{X_t, Y_t\}$ of continuous (ratio) variables is said to have a feed-forward loop relationship if both the following conditions are satisfied (see Fig 1)

A: Given X_t, Y_t and X_{t+1} are associated for all t (Fig 2a);

B: Given Y_t, X_t and Y_{t+1} are associated for all t (Fig 2b).

Consider Condition A: X_{t+1} and Y_t are associated. As Y_t is realized earlier than X_{t+1} , the former causes the latter, in the sense of Granger-causality (i.e. predictive causality¹¹). Similarly, in Condition B, X_t causes Y_{t+1} in the sense of Granger-causality. Fig. 2 illustrates both conditions separately, whereas Fig. 1 illustrates then together as a feed-forward loop. Assuming linearity and exchangeability, a feed-forward loop relationship can be described by the following equations

$$X_{t+1} = \beta_{1,1}X_t + \beta_{1,2}Y_t + \varepsilon_{1,t} \quad (1)$$

$$Y_{t+1} = \beta_{2,1}X_t + \beta_{2,2}Y_t + \varepsilon_{2,t} \quad (2)$$

where $t = 1, \dots, T$ are equally spaces time points and, $\beta_{i,j}$ ($i = 1, 2, j = 1, 2$) are parameters, and $\varepsilon_t = (\varepsilon_{1,t}, \varepsilon_{2,t})$ are independent and identically distributed (iid) bivariate normal random variables. Feed-forward loop is absent when at least one $\beta_{1,2}$ and $\beta_{2,1}$ are zero. (Eq. (1) and (2) are linearized versions of Conditions A and B respectively.) No intercept term is used because that would introduce a trend among X_t and Y_t . The above feed-forward loop model is described for continuous (ratio) variable X_t and Y_t . If X_t and/or Y_t are binary then the modeling Eqs. (1) and/or (2) can be modified by replacing X_{t+1} and/or Y_{t+1} in the left side with a multinomial logit link function.

$$\text{logit}(X_{t+1}) = \log_e \left(\frac{\Pr(X_{t+1}=1)}{\Pr(X_{t+1}=0)} \right) = \beta_{1,1}X_t + \beta_{1,2}Y_t + \varepsilon_{1,t} \quad (3)$$

$$\text{logit}(Y_{t+1}) = \log_e \left(\frac{\Pr(Y_{t+1}=1)}{\Pr(Y_{t+1}=0)} \right) = \beta_{2,1}X_t + \beta_{2,2}Y_t + \varepsilon_{2,t} \quad (4)$$

where $t = 1, \dots, T$ are equally spaces time points. In general, any appropriate link function can be used to modify Eqs. (1) and (2).

Assuming the above models, the parameters $\beta_{1,j}$ were estimated and the hypothesis of existence of feed-forward loop is tested using two different methods (described below), applying the theory in relationship to our hypothesis of a feed-forward relationship between variables. Both methods are appropriate ways of answering same questions: "Is there a feed-

forward loop between physical activity and physical performance? If there is, what is the nature of the loop?” The first method is based on fitting a regression model, and the second method is based on maximum likelihood estimation and likelihood ratio test. The first method is simpler and quicker to use than the second method, however, the second method is more efficient in terms of accuracy and power. Detecting feed-forward loop using both methods would increase confidence in the result.

In the first method, we fit the Eq. (1) & (2) (could be replaced (3) or (4) respectively) by Iterative Reweighted Least Squares (IRLS¹⁹). The use of IRLS is necessary to take into account the underlying dependence structure. We call this estimation the “feed-forward loop-regression estimation”. The data can be tested for feed-forward loop by fitting the above model and testing for significance of the parameters $\beta_{1,2}$ and $\beta_{2,1}$ using a Wald’s test. If both $\beta_{1,2}$ and $\beta_{2,1}$ are found to be significant, then existence of feed-forward loop will be concluded. Thus, if a maximum of p-values for $\beta_{1,2}$ and $\beta_{2,1}$ is less than the intended level of significance, only then the existence of feed-forward loop will be concluded. We call this test the “feed-forward loop-regression test”. This is our first method.

Note that, by comparing maximum of two p-values with level of significance, we are performing a conservative test. That is, in most cases the probability of Type I error is more than intended level of significance (5%). However, under some boundary conditions the probability of Type I error is exactly same as the level of significance and under no condition the probability of Type I error is less than the intended level of significance. Therefore, it is a valid test with level of significance 5%.

In the second method we used maximum likelihood estimation (MLE) for estimating the model parameters. To test for feed-forward loop a likelihood ratio test (LRT) is used to test for the hypotheses

$$H_0: (\beta_{1,2}, \beta_{2,1}) = 0 \text{ vs. } H_1: (\beta_{1,2}, \beta_{2,1}) \neq 0.$$

That is, a LRT statistics

$$T = -2 \log_e(L_0/L)$$

is computed which has a null distribution of χ^2 with 2 degrees of freedom. Here L_0 is the maximum likelihood under the assumption that $(\beta_{1,2}, \beta_{2,1}) = 0$, and L is the overall maximum likelihood (under so such assumption). We call this test the “feed-forward loop-LRT test”.

As the second method uses the exact LRT to test the hypotheses, it has more statistical power. Moreover, as mentioned above, the regression test is slightly conservative, which results in reduction in power. However, as the two tests exploits different characteristics of the data, the result from both tests would add to our knowledge. If we detect the feed-forward loop with both methods, then that would increase our confidence in existence of feed-forward loop. On the other hand if only one of the methods indicates existence of feed-forward loop, then feed-forward loop will still be concluded, but with less confidence.

Note that standardizing X_t and Y_t in Eqs. (1–4) with respect to other time-points would artificially introduce association across t . Therefore, it is advisable to not standardize X_t and Y_t unless such trend is desirable.

We applied our approach to physical activity and performance data from Women's Health and Aging Study II³. Five measures of physical activity were used: 1) physical activity (min/week); 2) total energy spent (kcal/week); 3) weight-adjusted total energy spent (kcal/day-kg); 4) energy spent doing lifestyle activities (kcal/week); and 5) energy spent doing exercise (kcal/week). Two measures of physical performance level were used: walking speed and grip strength. Each was measured at seven time points. Feed-forward loop analyses were performed between each physical activity measure and each physical performance level measure.

In some cases physical activity measures had zero values. Therefore, we carried out two sets of analysis: one with only non-zero physical activity values as continuous variables using Eqs. (1) and (2). Another sets of analyses were run using logistic regression, with a binary variable of positive-vs.-zero physical activity value replacing the actual physical activity value. For the latter case, Eq. of the form of Eq. (3) or (4) was used where of positive-vs.-zero physical activity value was the outcome.

While building the feed-forward loop models, the equations were fitted in the first three visits and last four simultaneously with same parameter values, but as separate loops (Fig. 4). This is because there was a large three-year gap between third and fourth visit, so we looked at the first three and last four as separate loops, while keeping the parameters the same (for a given set of measures). Thus, the same relationships were estimated using all the visits (given a set of measures), while separating the first three with last four (Fig. 4). Note that, in our analysis both physical activity and physical performance are used as outcome measures (as in a regression analysis built from Eqs. (1–4)) because these variables are outcomes of physical activity and physical performance values from an earlier time-point (Fig. 3).

Results

Baseline characteristics of the study population are shown in Table 1. The results of feed-forward loop-regression estimation and test are presented in Table 2 (for non-zero physical activity values as the physical activity outcomes) and Table 3 (for positive-vs.-zero physical activity value as the physical activity outcome), as per Fig. 3. First we used methods to assess the relationship between grip strength and physical activity with the feed-forward loop-regression test. The results detected a feed-forward loop relation between grip strength and physical activity. When physical activity was measured in kcal/week, min/week, kcal/day-kg and kcal/week lifestyle activity the relationships were significant (p-values: between 0.01 and 0.05). However, a feed-forward loop was not detected between grip strength and physical activity (measured as kcal/week spent in exercise). Using the second approach's LRT test, feed-forward loops were detected between grip strength and all five measures of physical activity ($p < 0.001$) for both types of physical activity outcome (non-zero physical activity values and positive-vs.-zero physical activity value).

Next, we tested for feed-forward loop between positive-vs.-zero physical activity value as physical activity level outcome and grip strength. Note that a zero kcal/week self-reported physical activity is equivalent to zero values in other measures (min/week or kcal/Day-kg). Therefore, we had only one measure of overall physical activity measured in kcal/week. Both feed-forward loop-regression and LRT tests indicated highly significant p-values ($p < 0.001$) for overall energy spent (kcal/week) and energy spent in lifestyle activities (kcal/week) between positive-vs.-zero physical activity value and grip strength. For energy spent in exercise activities (kcal/week), feed-forward loop-regression test indicated a borderline significant p-value (0.02) for existence of feed-forward loop with grip strength. However, the feed-forward loop-LRT test indicated a highly significant p-value ($p < 0.001$).

The differences between p-values in feed-forward loop-regression and feed-forward loop-LRT tests could be attributed to different method of fitting the models. Moreover, comparison between level of significance (0.05) and maximum of two p-values were used to perform the feed-forward loop-regression test, which resulted in a conservative test. Therefore, feed-forward loop-LRT tests were more accurate, had greater power and showed more significant p-values. However, except for energy measured as kcal/week exercise, the regression test and the LRT test agreed in all cases.

Next we evaluated for feed-forward loop relationships between walking speed and all five measures of physical activity among the visits where the subjects have positive physical activity values. When physical activity was measured in overall kcal/week, minutes per week in any physical activity, overall kcal/day-kg or kcal/week in lifestyle activities, a highly significant feed-forward loop was detected for each relationship ($p < 0.001$). A borderline significant p-value for feed-forward loop was detected between walking speed and overall kcal per week spent in exercise (0.04). From the positive regression coefficients, it follows that the association was also positive. Additionally, using the LRT test, feed-forward loops were detected between walking speed and all five measures of physical activity ($p < 0.001$).

Next, we tested for feed-forward loop between positive-vs.-zero physical activity value as physical activity level outcome and walking-speed using logit link function for positive-vs.-zero physical activity (with 1 for positive and 0 for zero). Both feed-forward loop-regression and LRT tests indicated highly significant p-values ($p < 0.001$) for overall energy spent (kcal/week) and energy spent in lifestyle activities (kcal/week). For energy spent in exercise activities (kcal/week) feed-forward loop-regression test indicated a borderline insignificant p-value (0.07) for existence of feed-forward loop with walking-speed. However, the feed-forward loop-LRT test indicated a highly significant p-value ($p < 0.001$).

Discussions

In this study, we have utilized preexisting statistical methods in novel statistical modeling of an example feed-forward loop; we have estimated the parameters of the feed-forward loop model and then formally tested for the existence of a feed-forward loop. We have provided empirical evidence for the presence of a feed-forward loop between physical activity and two physical performance measures (which are two components of formal definition of

frailty). A feed-forward loop between physical activity and physical performance implies that outcomes of heightening physical activity to improve not only physical performance, but multiple other systems and perhaps mitigate frailty. This is consistent with standing hypothesis and early evidence.

Notably, this approach may help fill in the methodological gaps for testing complex interactions between physiologic systems and frailty. Our use of the two-sided Granger-causality model is novel for aging data, and it is a much needed tool for testing complex interactions. Our ability to detect existence of feed-forward loop shows that our method is able to detect such loops from temporal multiple-variable observations.

Our results demonstrate and support the hypothesis that feed-forward loops do exist between measures of physical activity and grip strength or walking speed. From the coefficients of regression, it also follows that these two variables are positively associated with each other. Therefore, we conclude that physical activity and performance has 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) as opposed to being associated in a uni-directional manner. The results also suggest the existence of possibly larger loop structures connecting physical activity and performance with other mediating systems (such as loss of muscle mass and hormones).

Previous literature have demonstrated an association between physical activity and physical performance. However, many of these studies were cross-sectional, with few longitudinal studies. In this study, we examined the association between physical activity and physical performance using up to 7 waves of data over a 12-year follow-up period. With the rich WHAS II dataset, we found significant feed-forward loop relationships between physical activity and performance level. The strongest feed-forward loop relationship was between various measures of physical activity (physical activity min/week, energy spent kcal/week, kcal/day-kg and energy spent in lifestyle activities kcal/week) and walking speed. In these analyses we take a step towards answering the question “Is frailty the manifestation of faulty intercommunication between inadequately functioning biological systems, resulting in loss of homeostatic reserves and resilience to stressors?” We have provided empirical evidence for a feed-forward loop between two components of the frailty syndrome, such that physical inactivity does affect grip strength or walking speed and that reductions in these frailty components are worsened by mutual intercommunication. This builds on prior work proposing a vicious cycle of frailty^{4,17} and has criterion/content validity based on prior work on order of precedence.¹⁰

By studying the underlying feed-forward loop, we provide insight into how physical activity and performance jointly affect each other. These variables are positively associated in a feed-forward loop and have a snowballing effect on each other. Thus, a reduction in physical activity would not only degrade physical performance, but it would further reduce physical activity through declines in physical performance. If there are other mediating variables between physical activity and physical performance (e.g. muscle strength and/or hormones), deterioration in either of physical activity and physical performance will also worsen the mediators. For example, if muscle strength is a mediators between physical activity and

physical performance (i.e. physical inactivity decreases muscle strength⁷, and which in turn decreases physical performance, e.g. walking speed¹), then deterioration in either of physical activity and physical performance will decrease muscle strength as well. The novel use of analytic methods applied have permit going beyond prior evidence about pairwise or near associations to evaluate dynamics of a complex system. As physical activity and performance are components of frailty, reduction in physical activity or physical performance has a snowballing effect on overall development of frailty. These results provide empirical evidence that feed-forward loops are present in the phenotype of frailty, which is due to dysregulated energetics. Furthermore, it supports a priori hypothesis^{4,10} that the syndrome of frailty itself involves dynamical feed-forward loops that are dysregulated contributing to the vicious cycle found in the frailty phenotype.

In order to overcome a key limitation of modeling the multidirectional loop-structured system, we have used two-sided Granger-causality model to model and analyze the feed-forward loop structure. Using methods for testing for feed-forward loop relationship and estimating the equations representing such relationships, we have provided empirical evidence of feed-forward loop relationships between physical activity and performance levels. The broader implication methodologically is that we here introduce statistical modeling of feed-forward loop and the methods used for performing inference on the model as two-sided Granger-causality model. (*Note that, the feed-forward loop as we define is different from the concept of feedback loops used in biochemical systems.*) This model would be useful to test existence of feed-forward loops in other biological systems. Here we modeled a two-variable feed-forward loop. Similarly, three, four or multivariable feed-forward loop can be modeled by generalizing our model, which could then be applied to biological systems. Thus, our research is valuable for any biological systems where feed-forward loop modeling may arise.

This knowledge provides a stepping stone for uncovering and conclusively proving more complex systemic relationships driving the syndrome of frailty, such as between physical activity and other agents such as muscle mass, muscle strength, inflammation etc. The resulting insight into biologic dynamic systems and their dysregulation could then be used to design effective intervention in older adults. The methods implemented here for analyzing feed-forward loops are a significant development towards understanding the biology of multisystem dysregulation. Further, knowledge about feed-forward loops between two physiological agents can be used to build towards identifying critical targets for effective intervention in older adults. For example, if the feed-forward loop relationship is known then it would be possible to design an intervention in one physiological agent intended to affect both the agents. If a feed-forward relationship is established between any of the aforementioned variables then one agent (e.g. physical activity) could be the target of an intervention to improve all the variables in the loop (assuming that the system could indeed be reversed). If there are other mediating variables (e.g. muscle mass or hormone levels) between physical activity and physical performance, improvement in either of physical activity and physical performance will also positively impact the mediators; both specifically targeting and mediating effects could potentially decrease frailty. If more such complex intercommunications are established, then we might be able to create a “system-

map” of physiological systems and variables exhibiting a path leading to frailty; such a system-map can then be used to fully understand, prevent or treat and reverse frailty by designing interventions on the physiological systems that we determine to have highest influence on frailty.

In terms of the limitations to these conclusions, the major one is that resulting from use of self-report of physical activity, as measured by the Minnesota questionnaire. Subjective physical activity questionnaires may be inaccurate in older adults, who may under or overestimate participation due to poor recall, impaired cognition, and fluctuations in health or mood. Objective assessments of structured and unstructured physical activity may more accurately measure patterns of physical activity and energy expenditure in older adults. However, we used data that was collected over 7 visits period. Thus, we were able to capture the natural history of these relationships over a longer period of time. However, the analyses may have been limited by participant or survivor bias as participants who attended all 7 visits were likely healthier. Therefore, the feed forward loop estimated regressions were likely underestimated. On the other hand due to the 18 months’ gap between the visits (except for the gap between visits 3 to 4, which was 36 months), some of the influence of the prior visit may have been lost, resulting in further underestimation.

There are multiple possibilities for future research from our work. Methodologically, one can generalize our methods to model, analyze and detect general (with or without loops) complex systems for multisystem dysregulation. This can be done by setting up regression equations to represent a given system, and estimate or test for the parameters using our methods. More importantly, next-stage modeling and methodological development and new data, one can perform research to determine whether physical activity or performance level plays a bigger role in a feed-forward relationship, in the sense that one affects the outcome significantly more than the other. (For example, this can be done if we have a method of identifying the more influential component of the loop using denser observations.) The one with a bigger role would be a candidate for intervention (assuming that the system could indeed be reversed), as the target that would more efficiently affect both physical activity and performance level. Similarly, given a general complex system, one can identify the set of physiological agents having most influence in the system and seek to intervene in the optimal combination of agents for best results.

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Highlights

- We provide evidence for existence of feed-forward loop between physical activity and physical performance
- Our findings agree with the hypothesis that frailty is caused by interaction between malfunctioning biological systems
- We provide a model and a method for analyzing feed-forward loop in complex biological systems

Figure 1.
Feed-forward loop between X and Y

Figure 2.
Conditions A and B

Figure 3.
Feed-forward loop between physical activity and physical performance

Figure 4.
Feed-forward loop model in seven visits

Table 1

Baseline characteristics of the study population (n=431)

	Mean $\pm$ SD for Age and BMI; percentage (total number) for other variables
Age (yr)	73.9 $\pm$ 2.8
BMI (kg/m ²)	26.7 $\pm$ 5.2
Coronary artery disease	15% (66)
COPD	23% (99)
Diabetes	7% (32)
Osteoporosis	13% (57)
History of cancer	8% (36)
Mobility disability	31% (133)

Table 2

Results from testing for feed-forward loop and its parameter estimation using feed-forward loop-regression analyses (Fig. 3). The p-values used for computing the max p-values are underlined in the “p-value” column.

Y _t	grip-strength (X _t)					walking Speed (X _t)				
	max of p-values	Parameter Estimates				max of p-values	Parameter Estimates			
		Regressand	Var	coef, sd	p-value		Regressand	Var	coef, sd	p-value
physical activity min/week	0.049	X _{t+1}	X _t	0.91±0.006	<0.001	0.005	X _{t+1}	X _t	0.90±0.008	<0.001
			Y _t	0.001±3.4×10 ⁻⁴	0.049			Y _t	5.0×10 ⁻⁵ ±1.8×10 ⁻⁵	0.005
		Y _{t+1}	X _t	7.49±0.610	<0.001		Y _{t+1}	X _t	185.46±14.7	<0.001
			Y _t	0.37±0.032	<0.001			Y _t	0.36±0.032	<0.001
energy spent kcal /week	0.031	X _{t+1}	X _t	0.91±0.006	<0.001	0.007	X _{t+1}	X _t	0.90±0.008	<0.001
			Y _t	1.5×10 ⁻⁴ ±7.1×10 ⁻⁵	0.031			Y _t	1.0×10 ⁻⁵ ±3.7×10 ⁻⁶	0.007
		Y _{t+1}	X _t	37.41±2.87	<0.001		Y _{t+1}	X _t	876.70±68.4	<0.001
			Y _t	0.33±0.032	<0.001			Y _t	0.33±0.031	<0.001
energy spent kcal/day-kg	0.041	X _{t+1}	X _t	0.91±0.006	<0.001	0.006	X _{t+1}	X _t	0.90±0.008	<0.001
			Y _t	0.068±0.033	0.041			Y _t	0.004±0.002	0.006
		Y _{t+1}	X _t	0.076±0.006	<0.001		Y _{t+1}	X _t	1.87±0.146	<0.001
			Y _t	0.36±0.031	<0.001			Y _t	0.35±0.031	<0.001
kcal/week-lifestyle	0.011	X _{t+1}	X _t	0.91±0.006	<0.001	0.006	X _{t+1}	X _t	0.90±0.008	<0.001
			Y _t	2.4×10 ⁻⁴ ±9.3×10 ⁻⁵	0.011			Y _t	1.4×10 ⁻⁵ ±4.9×10 ⁻⁶	0.006
		Y _{t+1}	X _t	27.78±2.71	<0.001		Y _{t+1}	X _t	665.21±66.2	<0.001
			Y _t	0.28±0.039	<0.001			Y _t	0.28±0.038	<0.001
kcal/week-exercise	0.358	X _{t+1}	X _t	0.91±0.007	<0.001	0.044	X _{t+1}	X _t	0.90±0.009	<0.001
			Y _t	1.2×10 ⁻⁴ ±1.3×10 ⁻⁴	0.358			Y _t	1.4×10 ⁻⁵ ±7.1×10 ⁻⁶	0.044
		Y _{t+1}	X _t	20.77±2.36	<0.001		Y _{t+1}	X _t	479.47±55.1	<0.001
			Y _t	0.42±0.042	<0.001			Y _t	0.42±0.041	<0.001

Table 3

Results from testing for feed-forward loop and its parameter estimation using feed-forward loop-regression analyses (with positive vs. zero physical activity). The p-values used for computing the max p-values are underlined.

Y_t	grip-strength (X_t)					walking Speed (X_t)				
	Parameter Estimates					Parameter Estimates				
	max of p-values	Regressand	Var	coef, sd	p-value	max of p-values	Regressand	Var	coef, sd	p-value
Physical activity min/week	<0.001	X_{t+1}	X_t	0.72±0.017	<0.001	<0.001	X_{t+1}	X_t	0.79±0.014	<0.001
			Y_t	4.4±0.411	<0.001			Y_t	0.14±0.014	<0.001
		logit(Y_{t+1})	X_t	0.026±0.007	<0.001		logit(Y_{t+1})	X_t	8.2±0.178	<0.001
			Y_t	1.4±0.166	<0.001			Y_t	1.2±0.183	<0.001
kcal/week-lifestyle	<0.001	X_{t+1}	X_t	0.82±0.013	<0.001	<0.001	X_{t+1}	X_t	0.87±0.010	<0.001
			Y_t	2.1±0.353	<0.001			Y_t	0.068 ±0.011	<0.001
		logit(Y_{t+1})	X_t	0.027±0.004	<0.001		logit(Y_{t+1})	X_t	-0.74±0.109	<0.001
			Y_t	2.0±0.134	<0.001			Y_t	2.0±0.133	<0.001
kcal/week-exercise	0.020	X_{t+1}	X_t	0.83±0.011	<0.001	0.070	X_{t+1}	X_t	0.88±0.010	<0.001
			Y_t	1.9 ±0.326	<0.001			Y_t	0.046±0.011	<0.001
		logit(Y_{t+1})	X_t	-0.009 ±0.004	0.020		logit(Y_{t+1})	X_t	0.18±0.102	0.070
			Y_t	1.4±0.117	<0.001			Y_t	1.3±0.125	<0.001