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Going from bad to worse: A stochastic model of transitions in deficit accumulation, in relation to mortality

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Abstract

As people age, they accumulate deficits. The more deficits they accumulate, the greater their vulnerability, which can be expressed as the probability to accumulate even more deficits, or to die. The probability of death is known to be exponentially related to the number of deficits. Using data from elderly (aged 65+ years) participants in the Canadian Study of Health and Aging ($n = 9008$), we investigated the relationship between the number of deficits and the change in the number of deficits over two successive 5 year intervals. We show that the probabilities of changes in the number of deficits, in relation to baseline, are well fitted ($R^2 > 0.98$) by a simple distribution, with two parameters. The model suggests a maximum to deficit accumulation, and illustrates no level of deficit accumulation at which there is a net gain in fitness. Age-related deficit accumulation is highly characteristic, and can be modeled as a stochastic process with readily interpretable parameters.

Keywords: Ageing; Health transitions; Markov chain; Frailty

1. Introduction

As people age, they accumulate health problems. The problems encompass a broad range, from symptoms, clinical signs and laboratory abnormalities to diseases and disabilities, which can be jointly referred to as *deficits*. Even though people accumulate more deficits as they age, they do not accumulate the same deficits, nor do they accumulate their deficits at the same rate. How to understand differences in deficit accumulation is challenging. At the individual level, clinical medicine is devoted to precisely grading even seemingly very fine differences in which deficits a person has. Even though exactly which deficits a person has matters much to that individual, at a population level the meaning of these differences is surprisingly less clear, especially when many deficits are present. We have demonstrated that health status can be represented by combining deficits in an index variable, called the frailty index (Mitnitski et al., 2001, 2002). A higher number of deficits indicates a worse health state, and has a higher likelihood of an adverse health outcome, such as death or institutionalization (Mitnitski et al., 2004, 2005). Using data from different epidemiological and medical databases (11 sets from 4 countries, ~40,000 cases), we have shown that deficits accumulate exponentially with age, with an average relative rate of ~3% per annum (Mitnitski et al., 2005). This increase in deficit accumulation is comparable between datasets, even though we did not always consider the same variables, or even the same number of variables (we constructed frailty indices using from 20 to 130 variables). In each case, the frailty index better predicted mortality than did age, a finding that recently has been replicated (Goggins et al., 2005). That we can vary which variables we count, and how many we count, and still arrive at a replicable estimate of the rate of increase and of their combined lethality suggests that, at a population level, the exact nature of a given deficit to a person's state of health is less important than the deficit count (Mitnitski et al., 2005).

Simple counts combined as frailty indices are not just well correlated with adverse outcomes, but show other interesting properties. The statistical distribution of the frailty index changes with age. The frailty index goes from highly asymmetrical distributions at young ages (where relatively

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few deficits are prevalent) to less symmetrical distributions in old age (Rockwood et al., 2004). In short, at a population level, counting deficits is a robust way of summarizing the health states of individuals.

Despite these robust trends in estimating the average rates of deficit accumulation, and the shape of their distributions, little is known about quantitative aspects of transitions between different health states. Are health states relatively fixed? Do they generally increase with time, or do individuals transit significantly from a higher number of deficits to a lower number? Compared with the number of deficits, how does age influence the probability of transition between one state and another? Can stochastic processes be identified that model transitions between health states? Here, we consider transitional probabilities between discrete health states (represented by deficit counts) and their relation to the risk of death.

2. Methods

2.1. Population

The Canadian Study of Health and Aging (CSHA) is a representative cohort study designed to study dementia and other age-related problems, and described in detail elsewhere (Rockwood et al., 2001). Briefly, in 1990–1991, during the first wave of the study (CSHA-1) 9008 community-dwelling people age 65 and over were assessed using a self-report questionnaire, of whom complete data are available for 5586 survivors for the second wave (CSHA-2, conducted in 1995–1996) and 3211 for the third wave (CSHA-3, conducted in 2000–2001). Complete mortality follow-up is available, so we know that 1821 people died in the 60-month interval between CSHA-1 and CSHA-2, and an additional 1488 between CSHA-2 and CSHA-3. Thirty-one health related variables were available for each of the three waves of the study. The variables are almost evenly distributed between diseases and disabilities (Appendix A available at http://myweb.dal.ca/amitnits/mad-appendix.htm).

2.2. Statistical analysis

To estimate the parameters of the model and their confidence intervals, a nonlinear fitting procedure was used. The codes were written in Matlab 7.04 (Matworks Inc.). The parameters were estimated for each transition separately. Goodness of fit was evaluated using R^2.

3. Results

We considered the following stochastic model to describe the changes in individual health status as a Markov chain. We defined the health status of an individual as the number of deficits present, 'n'. Let P_{nk} be the probability that an individual with n deficits at a given assessment has 'k' deficits at the time of the next assessment, and let P_{nd} be the probability to die before the next assessment (i.e., the absorbing state). The transition probabilities between the different numbers of deficits can be approximated as follows,

$$P_{nk} = \frac{\rho_n^k}{k!} A_n, \tag{1}$$

where ρ_n and A_n are positive parameters that depend on the current state n. Evidently, for each n, the probabilities satisfy the conditions that:

$$\sum_k \frac{\rho_n^k}{k!} A_n + P_{nd} = 1 \tag{2}$$

and therefore

$$A_n = \frac{1 - P_{nd}}{\sum_k (\rho_n^k / k!)} \tag{3}$$

This formula can be simplified if we consider that k can change from 0 to infinity, and therefore

$$A_n = (1 - P_{nd}) e^{-\rho_n}. \tag{4}$$

In other words, for each n, the transition probabilities satisfy a Poisson law in which the parameter ρ depends on the current state n. Here, we consider a simple linear approximation for the parameter $\rho_n = a_1 + b_1 n$, and an exponential approximation for the probability of death (Mitnitski et al., 2005).

$$P_{nd} = e^{a_2 + b_2 n} \tag{5}$$

Therefore, the model is represented by n equations

$$P_{nk} = \frac{(a_1 + b_1 n)^k}{k!} e^{-(a_1 + b_1 n)} (1 - e^{a_2 + b_2 n}) \tag{6}$$

where the left side of the equations can be substituted with data (available at http://myweb.dal.ca/amitnits/mad-appendix.htm for the transitions between CSHA-1 and CSHA-2 and for the transitions from CSHA-2 to CSHA-3).

Because 31 deficits were available, the total number of states equals 33 (taking into account the states of no deficits and of death). A transition matrix shows the numbers of people at each transition (also available at http://myweb.dal.ca/amitnits/mad-appendix.htm). Of note, fewer than 4% of people had more than 11 deficits.

Table 1 shows the estimates of the parameters for the model for each of the two waves of follow-up (i.e. from CSHA-1 to

Table 1
Estimates of parameters, and goodness of fit, for the Markov chain relating transition probabilities and death to the number of deficits present

	CSHA-1, CSHA-2	CSHA-2, CSHA-3	Combined data
a_1	1.742 (1.633, 1.851)	1.801 (1.670, 1.934)	1.771 (1.671, 1.871)
b_1	0.849 (0.807, 0.890)	0.795 (0.744, 0.846)	0.823 (0.784, 0.862)
a_2	−2.158 (−2.252, −2.064)	−2.149 (−2.250, −2.047)	−2.153 (−2.235, −2.071)
b_2	0.149 (0.138, 0.161)	0.170 (0.157, 0.182)	0.160 (0.150, 0.170)
r	0.986	0.985	0.990
R^2	0.971	0.969	0.979

Parameters were estimated for the first and second transitions, and for a combined model.

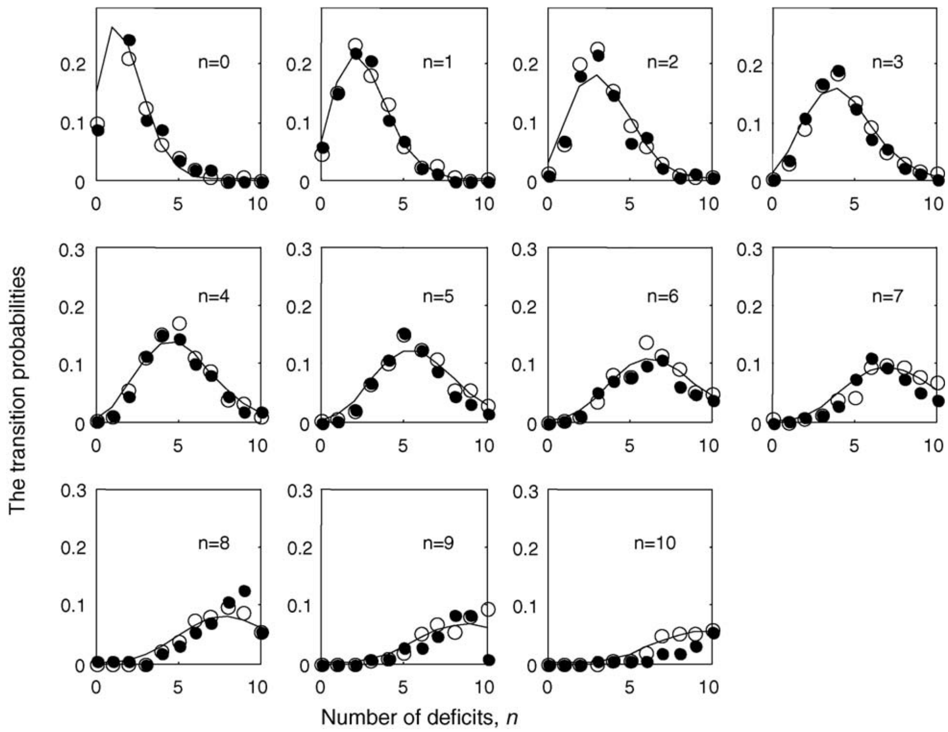

Fig. 1. The probability of transition from n to k deficits, in relation to the starting n deficits. Circles represent observational data of transitions from CSHA-1 to CSHA-2 (filled circles), and from CSHA-2 to CSHA-3 (empty circles). Estimates are presented for the model that combines transitions from CSHA-1 to CSHA-2, and from CSHA-2 to CSHA-3.

CSHA-2, and from CSHA-2 to CSHA-3) and for a combined model. Note that each is well fit, and further that the estimates are similar to each other, i.e., even though people are 5 years older, the relationships deficits, transitions and mortality remains virtually the same.

Even though some people show improvement (evidenced by having fewer deficits), the chance of having higher numbers of deficits increases with the number of deficits accumulated (Fig. 1). As the number of deficits accumulates, the risk of mortality increases exponentially (Fig. 2).

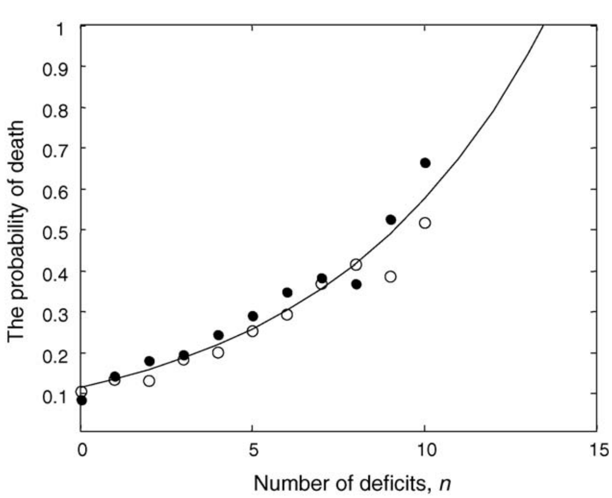

Fig. 2. The probability of death as a function of the number of deficits. Probability estimates come from the combined model of CSHA-1 to CSHA-2 (filled circles), and CSHA-2 to CSHA-3 (empty circles). Circles represent observational data and lines show the fit.

4. Discussion

Using data from a large population study, we have shown that transition probabilities between health states depend on the number of deficits accumulated in a simple model. The transition probabilities obey a simple law with very high accuracy ($R^2 = 0.98$). The interpretation of the parameters is straightforward. Two parameters are 'trivial' background components: $a_1 = \rho_0$ and $a_2 = \ln(P_{0d})$. For a person with n deficits at baseline, ρ_n is the expected average number of deficits at the next assessment. This expected average linearly increases (proportional to the number of deficits at the first assessment), such that $\rho_n = \rho_0 + b_1 n$; here $\rho_0 = 1.77$ (a constant, reflecting the average case with 0 baseline deficits) $+0.82n$, being the average increase with each additional deficit. For example, if a person had five deficits at baseline, the average expectation at the next assessment will be 6. For the absorbing state, the chance of dying P_{nd} also depends on the number of deficits at baseline $P_{0d} = \mathrm{e}^{a_2}$ ($P_{0\mathrm{d}} = 0.12$) and therefore $P_{nd} = P_{0d}\mathrm{e}^{b_2 n}$. Thus, a person with five deficits at baseline has a probability of dying of $0.12\mathrm{e}^{0.16\,(5)} = 0.27$. The chances to move to the state with zero deficits exponentially decreases with n: $P_{n0} = \mathrm{e}^{-(\rho_0 + b_1 n)}(1 - P_{0d}\mathrm{e}^{b_2 n})$.

Of some interest, the transitional probabilities remained unchanged between the two 5-year follow-up periods, even though the people being studied were 5 years older. This reinforces our earlier finding – recently replicated independently (Goggins et al., 2005) – that the number of deficits accumulated is more important in predicting mortality than is chronological age (Mitnitski et al., 2005).

The notion of deficit accumulation at the level of the individual is attractive. It accords with the idea of variability in aging being essentially related to stochastic processes that result in variable deficit accumulation at the subcellular, tissue and organ system levels (Kirkwood et al., 2005). Just as there are limits to viability with deficit accumulation at those levels, a limit to deficit accumulation appears here too. Of about 9000 starting subjects, we observed only 15 people with more than 17 of the 31 possible deficits at the first observation, and only 16 at the second observation. The theoretical limit is suggested by the ratio where $-a_2/b_2 = n$, at which $\exp(a_2 + b_2 n) = 1$, so that virtually no one survives to accumulate deficits beyond this maximum. Based on our data, the estimate maximum is 14 deficits (and the 95% confidence limit includes 17). Elsewhere, we have observed that this proportion (14/31) is in fact rarely seen in community-dwelling populations in developed countries (Mitnitski et al., 2005).

A Poisson distribution accommodates an infinite number of items. The nature of the items here (and the constraints that an individual can only either accumulate deficits or die, and that there is a practical limit to deficit accumulation without death) means that the model holds only for the most part, as is often the case with natural (cf. physical) phenomena. The basis of the practical limit to survival, given the accumulation of about half of any set of sufficiently health-relevant variables is here speculative. We note too that, some individuals can transit back to states with fewer deficits, consistent with the possibility of individual 'negative senescence' (Vaupel et al., 2004). Still, there is no net gain in fitness at any level, and no flattening of the curve that relates larger numbers of deficits to mortality.

A persisting and curious consequence of this approach is the usefulness of assuming equality of deficits. Within datasets, although qualitatively different types of deficits can be recognized (Ukraintseva and Yashin, 2001) and while the prediction of the individual risk of death is improved when the assumption of equality is relaxed (e.g., when items are weighted (Song et al., 2004)), a price is paid in generalizability (Mitnitski et al., 2005). Across different datasets, which have different designs, count different variables, and count different numbers of variables, the general properties of deficit accumulation nevertheless remain within narrow margins—e.g. they accumulate at the same rate, the rates are similarly related to death (Mitnitski et al., 2005), and deficit accumulations show similar patterns in the change of the coefficients of variation with age (Rockwood et al., 2004; Mitnitski and Rockwood, 2006).

It is not surprising that as people age, they accumulate deficits, and that the more deficits they accumulate, the more likely they are to accumulate even more, and to die; despite some people showing improvement, with age, things generally do go from bad to worse. It is intriguing that these general phenomena can be summarized in a simple model, with a few parameters that are easy to understand. Their additional elaboration is of interest, and is motivating further inquiries by our group.

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