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ORIGINAL ARTICLE

A poisson process model for hip fracture risk

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Abstract The primary method for assessing fracture risk in osteoporosis relies primarily on measurement of bone mass. Estimation of fracture risk is most often evaluated using logistic or proportional hazards models. Notwithstanding the success of these models, there is still much uncertainty as to who will or will not suffer a fracture. This has led to a search for other components besides mass that affect bone strength. The purpose of this paper is to introduce a new mechanistic stochastic model that characterizes the risk of hip fracture in an individual. A Poisson process is used to model the occurrence of falls, which are assumed to occur at a rate, λ. The load induced by a fall is assumed to be a random variable that has a Weibull probability distribution. The combination of falls together with loads leads to a compound Poisson process. By retaining only those occurrences of the compound Poisson process that result in a hip fracture, a thinned Poisson process is defined that itself is a Poisson process. The fall rate is modeled as an affine function of age, and hip strength is modeled as a power law function of bone mineral density (BMD). The risk of hip fracture can then be computed as a function of age and BMD. By extending the analysis to a Bayesian framework, the conditional densities of BMD given a prior fracture and no prior fracture can be computed and shown to be consistent with clinical observations. In addition, the conditional probabilities of fracture given a prior fracture and no prior fracture can also be computed, and also demonstrate results similar to clinical data. The model elucidates the fact that the hip fracture process is inherently random and improvements in hip strength estimation over and above that provided by BMD operate in a highly "noisy" environment and may therefore have little ability to impact clinical practice.

Keywords Fracture risk · Poisson process · Conditional probability · Bayesian analysis · Fall rate · BMD · DXA

1 Introduction

Osteoporosis is a significant health problem affecting more than 10 million people in the U.S. and more than 200 million worldwide [1, 50]. Osteoporosis is defined as the loss of bone mass with a concomitant disruption in microarchitecture, leading to an increased risk of fracture [14, 39]. The most common osteoporotic fractures occur at the wrist, spine, and hip. Hip fractures have a particularly negative impact on morbidity, as approximately 50% of the individuals suffering a hip fracture never live independently again [45]. Currently, there are about 1.6 million hip fractures worldwide, and the aging of the worldwide population is expected to increase the incidence of hip and other fractures due to osteoporosis [21, 25, 44, 45].

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The primary method for diagnosing osteoporosis and associated fracture risk relies on bone densitometry and the measurement of bone mass, as for example with dual-energy X-ray absorptiometry (DXA) [4, 33]. The use of bone mass is based on the well-established principles that bone strength is strongly related to the amount of bone material present and that a stronger bone in a given individual is associated generally with a lower fracture risk [27]. Indeed it has been shown that bone mass has about the same predictive power in predicting fractures as blood pressure has in predicting strokes [28]. Notwithstanding the positive correlation between bone mass and risk of fracture, there is still a great deal of uncertainty as to who will or will not actually suffer a fracture. For example, there are many individuals with higher bone mass that have a fracture and many individuals with lower bone mass that do not [53, 58]. It is also true that using the World Health Organization definition of osteoporosis (a T-score less than -2.5), the majority of hip fractures occurs in individuals who are not classified as "osteoporotic" [27, 28]. Because of the apparent inability of bone mass to predict who will or will not fracture, there has in recent years been an increased interest in "bone quality" [38]. In this context, it is surmised that other tissue-specific factors such as architecture, geometry, micro-damage, and degree of bone mineralization may have an impact on bone strength and thus allow a greater degree of predictability for fracture and non-fracture outcomes [16, 59, 61, 64].

Estimation of fracture risk is most often evaluated using logistic or proportional hazards models [16, 23, 27, 28, 53, 58, 61]. These and related approaches are statistical regression techniques that use a set of independent variables (e.g., bone mineral density (BMD), age, gender, weight, height) to estimate a dependent variable (e.g., risk or relative risk of fracture). By incorporating both bone factors (e.g., BMD) and non-bone factors (e.g., age, weight and height), proportional hazards and logistic regression models have provided adequate estimates of fracture risk. However, these analyses do not have an underlying physical model of the overall fracture process. Therefore, they cannot offer a mechanistic understanding of *why* certain individuals fracture and the role that the underlying variables may play. For example, one of the most important predictive variables in fracture risk is the presence or not of a prior fragility fracture. Regression based analyses do indeed demonstrate a significant increase in fracture risk with the existence of a prior fragility fracture [36]. However, since such an analysis does not provide a physical understanding of the underlying nature of the process by which an individual sustains a fracture, it does not "explain" why a prior fracture has such a strong impact on fracture risk.

The purpose of this paper is to introduce a new mechanistic model that characterizes the risk of hip fracture in an individual. In particular, a new stochastic model that provides a quantitative measure of the risk of hip fracture as a function of BMD and a person's underlying risk of falling will be presented. It will be shown how certain relationships, for example, as exists between BMD, age, and fracture risk can be explained by the new model. The model will also be used to demonstrate why the bone mineral densities associated with fracture and non-fracture groups overlap to a relatively large extent. It will also be shown that the new model explains *why* the existence of a prior fracture leads to an increase in fracture risk. Lastly, some suggestions are provided for future work that will be needed in order to validate and to clinically utilize the proposed model.

2 Methods

2.1 Non-Bayesian model

In order to quantitatively model the probability or risk of a hip fracture in a given individual, it is first noted that 90–95% of hip fractures occur as a result of a fall [32, 62]. Here it is assumed that all hip fractures occur as a result of a fall. A fall, however, is no guarantee of a hip fracture; indeed only about 5% of falls result in a fracture [62]. Using this framework, the following probabilistic model for the occurrence of a hip fracture is hypothesized.

The model assumes that an individual falls in accordance with a Poisson process at rate λ per year [55]. This means that the probability of k falls in the time interval $(0,T]$, where 0 is an (arbitrary) time of initial observation and T is the length in time of the specified interval, is given by

$$P(k \text{ falls in } (0,T]) = \frac{e^{-\lambda T}(\lambda T)^k}{k!} \quad k = 0, 1, \ldots, \tag{1}$$

Having a fall, as noted earlier, is no guarantee of a hip fracture. This is because the load induced on the hip in a fall may not be sufficient to cause a fracture. In addition, the load induced on the hip will be different for each fall. Therefore, in order to extend the stochastic fall model to characterizing fracture risk, each fall, i, is associated with a random load L_i. The sequence of loads L_1, L_2,… are assumed to be independent, identically distributed random variables, having distribution function $F(\cdot)$ and statistically independent of the fall process. The combined process is known as a compound Poisson process [63]. As may be seen in Fig. 1, the height of each line segment varies to reflect the fact that each fall induces a distinct load. A fracture occurs at the ith fall if load L_i exceeds the strength, S, of the hip in a given individual. The strength, S, is shown as the dashed line in Fig. 1, and will in the following assumed to be a deterministic function of BMD.

It is convenient to denote the probability of a hip fracture (denoted by "fx") conditioned on a fall having occurred by p_S, i.e.,

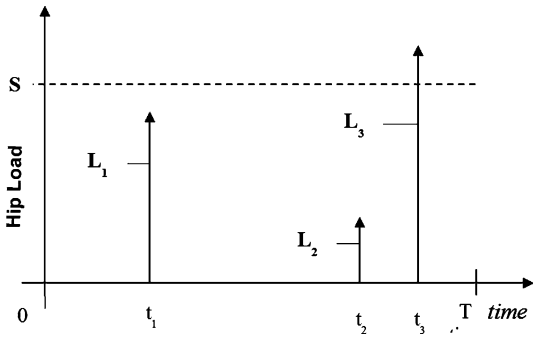

Fig. 1 A compound Poisson process model is shown for falls that induce a random load, L, on the hip. The height of each *arrow* varies to indicate that each load induced by a fall is distinct. The *dashed horizontal line* indicates the strength, S, of the hip. In this figure only the load L_3 that occurs as a result of a fall at time t_3 results in a fracture

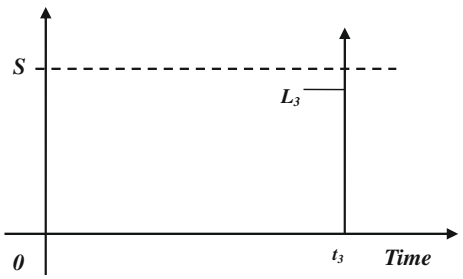

Fig. 2 A thinned Poisson process (associated with Fig. 1) is shown that is the result of retaining only those falls that result in a fracture. The thinned Poisson process is itself a Poisson process with an arrival rate equal to $\lambda_{\text{thinned}} = \lambda \times p_S$, where p_S is the probability of a fracture conditioned on a fall having occurred (see text). The *dashed horizontal line* indicates the strength, S, of the hip

$$p_S = \Pr(fx|\text{Fall}) = \Pr(L > S) \tag{2}$$

In (2), L denotes a generic element of the sequence $\{L_i, i = 1, 2, \ldots\}$. Thus, the compound Poisson process as defined here is a Poisson process which has associated with each event a probability of a fracture, p_S. It is then possible to extract from this compound Poisson process a *thinned* (*Poisson*) *process* [15]. In this case, the thinned process is defined by retaining *only the falls that result in a fracture in a given time interval, if there is one*. For example, Fig. 2 displays the thinned process associated with the realization shown in Fig. 1. As may be seen, only one event is retained in the thinned Poisson process from the compound Poisson process of Fig. 1, namely the fall that occurred at $t = t_3$ that produced a load L_3 that was greater than the hip strength, S, during the interval of observation, $(0,T]$. Using an extremely convenient feature of a thinned compound Poisson process, it is possible to characterize a number of statistical features relevant to quantitative fracture risk. *This is because the thinned process is itself a Poisson process, so that the occurrence of an event, where an event is now defined to be a fall that results in a fracture, also occurs according to a standard Poisson process but whose associated rate, $\lambda_{thinned}$, is given by* [15]

$$\lambda_{\text{thinned}} = \lambda \cdot p_S \tag{3}$$

Thus, the stochastic process that describes the falls which result in fractures is characterized completely by the rate parameter λ_{thinned}. For instance, the probability of no fracture occurring in the observed interval $(0,T]$ is given by

$$\Pr(\text{no } fx \text{ in } (0,T]) = e^{-\lambda_{\text{thinned}} T} = e^{-\lambda p_s T} \tag{4}$$

Similarly, the probability of at least one fracture in $(0,T]$ is given by

$$\Pr(fx \text{ in } (0,T]) = 1 - e^{-\lambda_{\text{thinned}} T} = 1 - e^{-\lambda p_s T} \tag{5}$$

To apply the model (3–5) to individual subjects, information on the fall rate and conditional probability of fracture are required. First, consider the fall rate, λ; this parameter contains *all the information regarding the likelihood of a fall in a given time period for a given individual*. In general, the fall rate would have to be estimated for any given person. As a first approximation and for purposes of exposition of the proposed model, it is reasonable to assume that the main influence on fall rate is age. Indeed there is much information on the incidence of falls as a function of age, which in an adult increases significantly over the decades of life [18, 32]. There are of course numerous other factors besides age per se which relate to fall rate, but this subject—that is how to estimate fall rate in an individual—is not addressed in this paper.[1] Since low-trauma hip fractures rarely occur without the occurrence of a fall, it is clear that the stochastic nature of falls must be incorporated into any model for hip fracture risk. A specific dependence of fall rate on age will be given below.

Second, consider the load, L. The load applied to a hip is dependent on several factors, some of which may be known and some unknown a priori. An unknown factor, for example, is the direction of fall, such as a fall to the side or back or to the front, which is well known to play a major role in the level of induced load on the hip [49]. In addition, certain known factors such as height, weight, and age may also play a role in the induced load. Height, for example, is related to a fall's potential energy. Weight can be related both to the associated potential energy and to the (opposing) cushioning effect that soft tissue over the hip may impart [54, 65]. Age may also have an impact on the ability of an individual to cushion the impact to the hip, for

[1] Indeed age is a proxy for several *physiologic* factors such as vision, stability, impaired mental status, and frailty, which together with environmental factors (e.g., steps, carpets, cords, ice) should to as much an extent as possible be factored into the evaluation of an individual's fall rate, λ.

example by reacting with an outstretched hand or by another neuromuscular reaction (e.g., muscle tightening), perhaps local to the hip or more generally [18].

Although the load that occurs as a result of a fall is clearly random, there is presently relatively little empirical evidence about the specific form of the associated probability distribution function. There is also relatively little information on how height, weight, age, and mental status, among other factors, may be explicitly incorporated into the conditional probability function (2). In order to deal with this lack of knowledge, the conditional probability, p_S, is characterized here by a parameterized distribution function, namely the Weibull distribution given by [48]

$$F(y) = 1 - e^{-\left(\frac{y}{\beta}\right)^{\alpha}}, \quad y \geq 0 \tag{6}$$

As may be seen, the Weibull distribution is specified by two parameters, a scale parameter, β, and a power parameter, α, and as such provides sufficient degrees of freedom to model a wide range of observed statistical data [37].

As mentioned above, the underlying model stipulates that loads $\{L_1, L_2, \ldots\}$ are independent random variables identically distributed according to (6). Therefore, it follows immediately from (2) and (6) that p_S is given by

$$p_S = e^{-\left(\frac{s}{\beta}\right)^{\alpha}} \tag{7}$$

A plot of p_S as a function of strength, S, for several choices of the parameter α with $\beta = 1$ is shown in Fig. 3. Note that β is a scale parameter and serves to "select" a particular portion of the displayed curve, which is plotted over a wide range of (dimensionless) strength values, S. As a probability, it ranges from a minimum of zero (achieved when strength equals infinity and a fall will never result in a hip fracture) to one (achieved when strength equals zero and a fall will always result in a hip fracture).

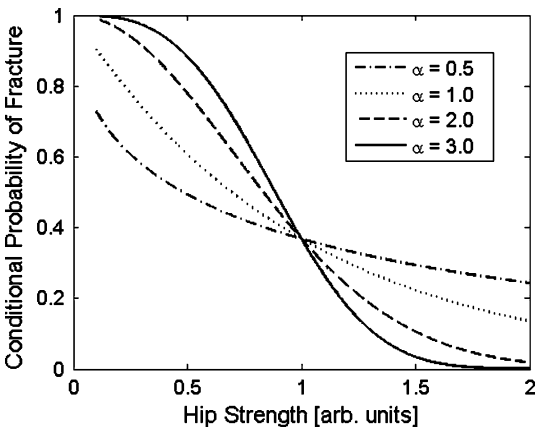

Fig. 3 The probability of fracture conditioned on a fall having occurred as a function of strength, S, and for various values of the parameter, α, using the Weibull probability density function, with $\beta = 1$ (Eq. 7). As may be seen, the conditional probability is a monotonically decreasing function as strength increases

As a further step towards modeling an individual's risk of fracture, it is useful to model the strength, S, of the hip as a function of its BMD, which is denoted by ρ. Numerous experimental studies have demonstrated that the strength of bone can be related to its BMD by a power law function [3, 7, 10, 40, 51]:

$$S = k\rho^{\gamma} \tag{8}$$

In (8), k and γ are constants dependent on the specific experimental conditions (for example, specific geometry and architecture of the specimen being tested [35, 64]). Although for regularly shaped specimens of bone (e.g., trabecular bone cubes) the exponent γ has been shown to lie between two and three, for intact proximal femurs that are tested to failure the exponent is smaller (between one and two) [3, 7, 40]. This may be a result of the different "densities" employed. In the testing of trabecular bone samples, for example, the density used is usually proportional to the true volumetric density. However, in many of the studies involving the evaluation of the strength of intact femurs, the density is most often the bone mineral content or areal BMD, both of which can be obtained using DXA. Another reason for distinct parameter values may be related to the testing of regularly shaped specimens versus the testing of whole (intact) bones. In any case the model of (8) does provide a reasonable estimate of strength by the proper selection of the associated parameters. Substituting (8) into (7) allows p_S to be expressed as a function of ρ

$$p_S = e^{-\left(\frac{\rho}{\beta}\right)^{\alpha}} \tag{9}$$

Note that in (9) the values for the constants in α and β are distinct from the values of the constants in (7), but for simplicity we have used the same symbols since the form of the expression is the same.

Using the above expressions, the probability of at least one fracture occurring in the time interval $(0,T]$ can then be expressed as a function of the person-specific fall rate and BMD, ρ:[2]

[2] The remainder of this paper will refer only to the occurrence of no fracture or at least one fracture in a time interval $(0,T]$, because of the relative simple forms of the expressions in (4) and (5). However, because of the relative rarity of a fracture event, the probability of at least one fracture will generally be close to the probability of exactly one fracture, in a given time interval. In any event, the exact expressions can easily be substituted if preferred.

$$\Pr(fx \text{ in } (0,T]) = 1 - e^{-\lambda T e^{-\left(\frac{\rho}{\beta}\right)^{\alpha}}} \tag{10a}$$

Similarly, the probability of no fracture occurring in (0,T] can be expressed as

$$\Pr(\text{no } fx \text{ in } (0,T]) = e^{-\lambda T e^{-\left(\frac{\rho}{\beta}\right)^{\alpha}}} \tag{10b}$$

Equation 10a can be used to generate a set of fracture probabilities for a variety of fall rates and bone mineral densities. To do this, the fall rate is assumed to be an affine function of age, $\lambda = \lambda_{\text{age}}$, according to:

$$\lambda_{\text{age}} = a \cdot \text{age} + b \tag{11}$$

A number of studies have reported on age-dependent falls in a variety of populations; from this data we estimated values of a and b for an age range limited to 40–90 years [20, 31, 32]. In this study, $a = 0.02$ and $b = -0.7$. This produced for example, a fall rate of $\lambda_{40} = 0.1$/year (or 1 fall in a period of 10 years on average) and a fall rate of $\lambda_{90} = 1.1$/year (or 1 fall in a period of about 0.9 year on average). For this computation, the BMD ranged between 0.2 and 0.7 g/cm^2, in accord with the variations observed in a population of women measured at the hip with DXA [47].

The relative risk (RR) of fracture between two groups of individuals having distinct fall rates (λ_1 and λ_2, respectively) and BMD's (ρ_1 and ρ_2, respectively) over an interval of observation, T, can also be determined, namely as follows:

$$\text{RR} = \frac{1 - e^{-\lambda_1 T e^{-\left(\frac{\rho_1}{\beta}\right)^{\alpha}}}}{1 - e^{-\lambda_2 T e^{-\left(\frac{\rho_2}{\beta}\right)^{\alpha}}}} \tag{12}$$

2.2 Bayesian model

The model presented in the previous section assumed that the underlying parameters, i.e., the fall rate, λ, and the BMD, ρ, were fixed and non-random. This means that for a given individual with fall rate and BMD known a priori, all the probabilities and statistics relevant to hip fracture can be computed. Alternatively, it is also possible to take a different and somewhat more practical perspective. In this approach, the fall rate and BMD associated with a given ensemble of individuals are assumed to be random variables. Generally, the distribution of these random variables, or some aspect of the distribution such as the means and variances may be parameterized by an appropriate set of variables, which are measurable or otherwise known a priori (such as age). This viewpoint is consistent with the clinical environment in which a patient is seen by a physician and for whom no knowledge of fall rate and/or BMD may be available. Thus, a patient may be considered to exist within an ensemble of subjects, and onto which a probabilistic framework is placed.

The extension to such a probabilistic framework for the fall rate and BMD allows the model to address two key observations in clinical osteoporosis research for which no analytic understanding is presently available. Extension of the model to include random parameters will be explained in the context of addressing these two key observations.

The first observation is the oft-stated fact that "there are many individuals who have low bone mass but do not fracture while there are many individuals who have higher mass but do." (See for example [6, 42, 43, 47, 67] for just a small sampling of the recent literature.) This observation is often used as an underlying hypothesis for research seeking other bone but non-mass factors (such as architecture and geometry for example) that can explain this "somewhat confounding" observation. However the thinned Poisson process model can be extended to analyze and explain this first observation without introducing additional "bone quality" factors as follows. To do this, assume that the BMD, ρ, of each individual in a group of individuals is distributed as a Normal random variable with mean, μ, and variance, σ^2, i.e., $\rho \sim N(\mu, \sigma^2) \equiv g(\rho)$. This may for example, be based on the set of NHANES data that characterizes the mean and variance of BMD as a function of age, gender, and ethnicity [12, 41]. Assume further that each individual in the group has a fixed (non-random) value of fall rate, λ_0. Then it is possible using Bayes' rule to compute the conditional probability density function, $f(\rho|\text{no fracture in } (0,T])$, that is the conditional probability density of BMD conditioned on not having a fracture in the time interval (0,T], as follows [66]:

$$f(\rho | fx \notin (0,T]) \propto e^{-\lambda_0 T e^{-(\rho/\beta)^{\alpha}}} \cdot g(\rho) \tag{13}$$

Using a similar analysis, an expression for the conditional probability density function, $f(\rho|fx \text{ in } (0,T])$, that is the conditional probability density of BMD conditioned on having a fracture in the time interval (0,T], can be shown to be given by

$$f(\rho | fx \in (0,T]) \propto \left(1 - e^{-\lambda_0 T e^{-(\rho/\beta)^{\alpha}}}\right) \cdot g(\rho). \tag{14}$$

Results using these expressions (13), (14) are provided in the next section.

The second key observation to be analyzed in the context of the present model is that a prior osteoporotic fracture is one of the most significant risk factors that an individual will suffer another one [11, 26, 29, 36]. The Poisson process model can help to illuminate *why* this is so. The probability that an individual has a fracture in the interval (T,2T] given a fracture in the interval (0,T] can be expressed, again using Bayes' formula, as

$$\Pr(fx \in (T, 2T] | fx \in (0, T]) = \frac{\Pr(fx \in (T, 2T], fx \in (0, T])}{\Pr(fx \in (0, T])}. \tag{15}$$

In this analysis, the BMD is assumed known (e.g., measured), and the fall rate, λ, is assumed to be a random variable. (This is a common clinical situation in which a patient has received a DXA scan but there is a relatively large uncertainty in the underlying fall rate.) To simplify the analysis, the probability distribution, $f_\lambda(x)$, for the fall rate is assumed to be uniform, i.e.,

$$f_\lambda(x) = \begin{cases} \dfrac{1}{\lambda_2 - \lambda_1}, \lambda_1 \le x \le \lambda_2; & 0, \text{ otherwise.} \end{cases} \tag{16}$$

In (16), λ_1 and λ_2 are the lower and upper limits, respectively, of the uniform distribution. This would be equivalent to having a complete lack of knowledge of a person's likelihood of falling short of bounding it from below and above. The right side of (15) can then be computed by averaging over the fall rate

$$\Pr(fx \in (T, 2T] | fx \in (0, T]) = \frac{\int_{\lambda_1}^{\lambda_2} \left(1 - e^{-\lambda T e^{-(\rho/\beta)^\alpha}}\right)^2 \mathrm{d}\lambda}{\int_{\lambda_1}^{\lambda_2} \left(1 - e^{-\lambda T e^{-(\rho/\beta)^\alpha}}\right) \mathrm{d}\lambda} \tag{17}$$

A similar analysis can be carried out for obtaining the probability that an individual has a fracture in the interval $(T,2T]$ given no fracture in $(0,T]$. This conditional probability, expressed as

$$\Pr(fx \in (T, 2T] | fx \notin (0, T]) = \frac{\Pr(fx \in (T, 2T], fx \notin (0, T])}{\Pr(fx \notin (0, T])} \tag{18}$$

can then be computed with an expression analogous to (17):

$$\Pr(fx \in (T, 2T] | fx \notin (0, T]) = \frac{\int_{\lambda_1}^{\lambda_2} \left(1 - e^{-\lambda T e^{-(\rho/\beta)^\alpha}}\right) \cdot e^{-\lambda T e^{-(\rho/\beta)^\alpha}} \mathrm{d}\lambda}{\int_{\lambda_1}^{\lambda_2} \left(e^{-\lambda T e^{-(\rho/\beta)^\alpha}}\right) \mathrm{d}\lambda} \tag{19}$$

Equations 17 and 19 can be solved analytically, and the results are also provided in the next section. As will be demonstrated, the existence of a prior fracture biases the value of the conditional probability in (17) towards higher values; it does this through an implicit expectation that the fall rate is higher compared with a group of individuals with the same underlying a priori distribution but who did not have a prior fracture, biasing the conditional distribution of (19) towards lower values.

It is also possible to extend this analysis to individuals whose fall rate and BMD are *both* unknown and characterized with associated probability distributions (based on age, for example). In this case, it is expected that there would be an even greater increase in fracture risk in the prior fracture group as compared with the group with no prior fracture. This is because the conditional distribution of a fracture based on a history of prior fracture will bias both the fall rate and BMD towards values which increase fracture risk (i.e., higher fall rate and lower BMD) while no history of fracture will bias both fall rate and BMD towards values which decrease fracture risk.

It is worthwhile to examine one additional aspect of the model in the context of hypothesis testing. The sensitivity and specificity of a hypothesis testing scheme in order to classify a subject as a fracture (hypothesis 1 or "H_1") case or a non-fracture (hypothesis 0 or "H_0") case is well known in osteoporosis research [2, 4]. In general, the performance of a hypothesis test can be assessed through a receiver operating characteristic (ROC) curve, and in particular through the area under the ROC curve (AUC) [66]. In osteoporosis, typical values for AUC in clinical studies are in the range of 0.7–0.8. The search for additional bone quality factors is directed at least in part towards improving the efficiency of diagnosing osteoporosis (i.e., increasing AUC values), so that individuals who will experience a low-trauma fracture can be correctly identified ("sensitivity"), while those who will not suffer a fracture not be identified as a future fracture case ("specificity"). In the context of the present model, consider two cases. In the first, assume that the fall rate and BMD are both random variables, and that both are observed. In the second, assume again that fall rate and BMD are both random variables, but that only BMD is observed. The two respective ROC curves can be evaluated as follows, in the context again of a Bayesian analysis.

It can be readily shown using Bayes' law that the joint probabilities, $f_1(\rho,\lambda|H_1)$, $f_0(\rho,\lambda|H_0)$, of BMD (ρ) and fall rate (λ) under H_1 and H_0, respectively, are given by

$$f_1(\rho, \lambda | H_1) = \frac{\left(1 - e^{-\lambda T e^{-\left(\frac{\rho}{\beta}\right)^\alpha}}\right) g(\rho) h(\lambda)}{\Pr(H_1)} \tag{20}$$

$$f_0(\rho, \lambda | H_0) = \frac{e^{-\lambda T e^{-\left(\frac{\rho}{\beta}\right)^\alpha}} g(\rho) h(\lambda)}{\Pr(H_0)} \tag{21}$$

In (20) and (21), $g(\rho)$ and $h(\lambda)$ are the a priori probability density functions of ρ and λ, respectively, where they are also assumed to be independent of one another, and $\Pr(H_1)$ and $\Pr(H_0)$ are the a priori probabilities of H_1 and H_0, respectively.

For the case where both ρ and λ are observed, a likelihood ratio, Λ_2, is formed by dividing (20) by (21), taking

the natural logarithm and retaining only those terms dependent on the measurements, ρ and λ [66]:

$$\Lambda_2 = \lambda e^{-\left(\frac{\rho}{\beta}\right)^{\alpha}} \tag{22}$$

A ROC curve can be formed by evaluating the probabilities of Λ_2 conditioned on H_1 and H_0, respectively, to be greater than a threshold parameter, η, which varies over a suitably large range of positive values.

An entirely analogous procedure can be used to determine the ROC curve for the single measurement (ρ only) case. To do this, the probabilities of ρ conditioned on H_1 and H_0 are determined by integrating (20) and (21), respectively, with respect to the fall rate, λ. Again, a likelihood ratio, Λ_1 is formed and the probabilities of Λ_1 conditioned on H_1 and H_0, respectively, to be greater than a threshold parameter, η, which varies over a suitably large range of positive values, are computed. This analysis was carried out to determine the two ROC curves, using the following set of parameters. The a priori probability density for the BMD was assumed normal with a mean of 0.75 g/cm^2 and a standard deviation of 0.2 g/cm^2. The a priori probability density for the fall rate λ was assumed to be uniform as in (16), with $\lambda_1 = 0.05$/year and $\lambda_2 = 5$/year. The other parameters were: $\alpha = 1.55$, $\beta = 0.4$ g/cm^2, and $T = 3$ years.

3 Results

3.1 Non-Bayesian model

Figure 4 displays the probability of fracture over a time period of 1 year at each decade of age, as a function of BMD, which was evaluated using (10a) and (11). Figure 5 displays the RR (12) for individuals having identical fall rates ($\lambda = 0.5$/year) but with ρ_1 varying between $\rho_2/2$ and

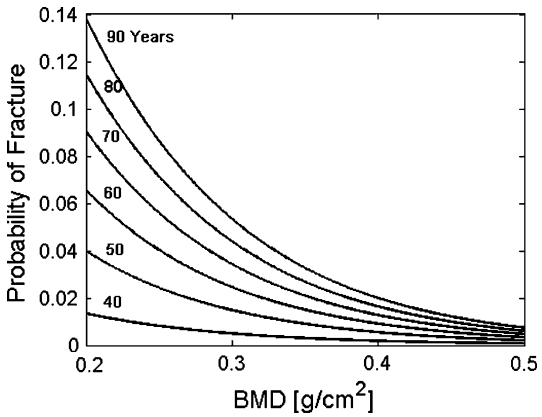

Fig. 4 The probability of fracture as a function of BMD, for individuals of ages 40, 50, 60, 70, 80, and 90 (Eqs. 10a). The fall rate is assumed to be an affine function of age (Eq. 11)

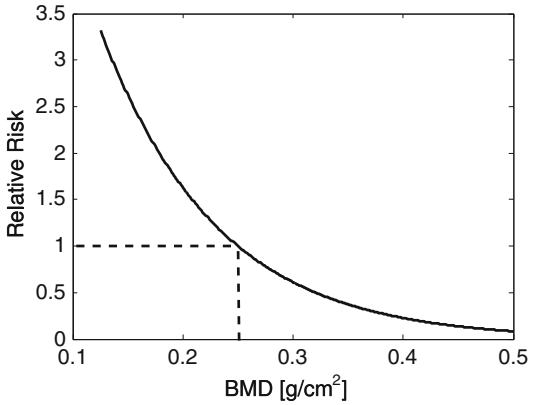

Fig. 5 The RR of hip fracture (Eq. 12) for individuals of varying BMD compared to a reference individual with the same fall rate ($\lambda = 0.5$/year) but with a BMD of 0.25 g/cm^2. The *dashed lines* indicate that the RR is one at this density value (0.25 g/cm^2)

$2 \times \rho_2$, and $\rho_2 = 0.25$ g/cm^2, with $\alpha = 1$, $\beta = 0.1$ g/cm^2 and $T = 1$ year.

3.2 Bayesian model

The two conditional probability functions, (13) and (14), using $\lambda_0 = 0.5$/year, $\beta = 0.1$ g/cm^2, $\alpha = 1.5$, $\mu = 0.4$ g/cm^2, $\sigma = 0.22$ g/cm^2, and $T = 1$ year are plotted in Fig. 6. As may be seen, there is considerable overlap in the two conditional probability densities, which arises as a *natural outcome of the stochastic nature of the underlying process by which hip fractures occur*. No additional bone quality factors were used to derive this result; indeed there is *no*

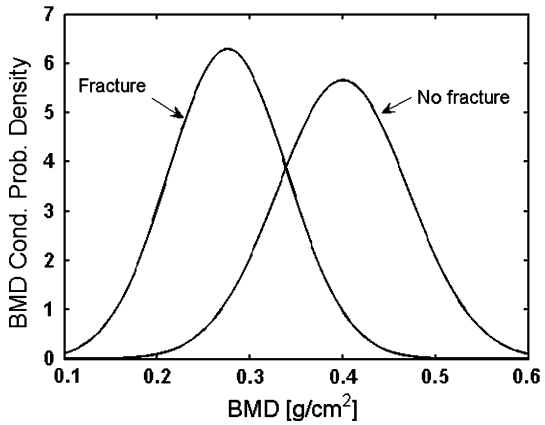

Fig. 6 The conditional probability density functions of BMD for subjects who have and have not had a fracture in a time period $(0,T]$, respectively (Eqs. 13 and 14). As may be seen there is considerable overlap between the two distributions, analogous to clinical observations. This overlap is often used as a basis to search for other bone parameters that can improve estimates of bone strength (over and above using BMD alone). In this study, bone strength is assumed known and the overlap arises from the inherent stochastic nature of the hip fracture process, which includes the randomness of fall occurrences and the randomness of induced loads at the hip

uncertainty in knowledge of bone strength as may be seen from (8). Note that the fall rate (which was assumed to be identical in the two conditional distributions) could also be a random variable with a given distribution; in this case, the overlap of the two conditional distributions (which can also be computed using Bayes' rule) would be expected to increase even further.

Figure 7 presents the conditional probabilities of fracture, given a prior fracture (17) and no prior fracture (19), respectively. The data was generated for a range of densities from 0.01 g/cm^2 to 0.3 g/cm^2, $\alpha = 1.6$, $\beta = 0.1$ g/cm^2, $\lambda_1 = 0.05$/year, $\lambda_2 = 3$/year, and $T = 1$ year. Figure 8 displays the ratio of the two conditional probabilities, demonstrating that there is a significant density-dependent increase induced in the conditional probability of fracture by the existence of a prior fracture relative to the conditional probability of fracture by the lack of a prior fracture.

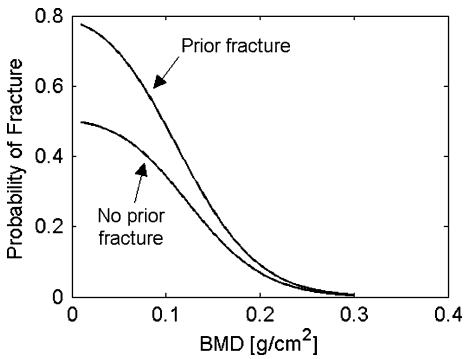

Fig. 7 The conditional probabilities of fracture in the interval (T,2T], given no prior fracture in (0,T], and given at least one prior fracture in (0,T] (Eqs. 17 and 19). As may be seen there is a significant increase in the probability of a fracture given the occurrence of a prior fracture, particularly in the lower BMD range. This result is largely in agreement with clinical data; the thinned Poisson process model for hip fractures provides a basis by which to understand this key clinical observation

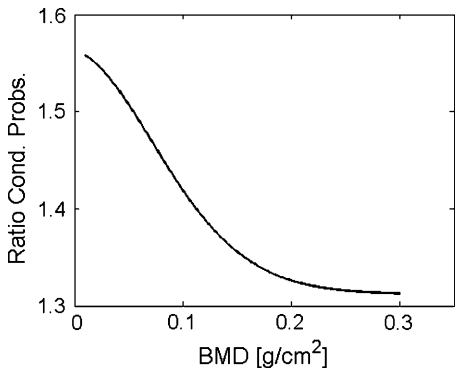

Fig. 8 The ratio of the probabilities of hip fracture, conditioned on a prior fracture and no prior fracture, using the data in Fig. 7. The ratio depends on BMD, with the lowest density values associated with about a 56% increase in hip fracture risk, and the highest density values associated with about a 32% increase in hip fracture risk

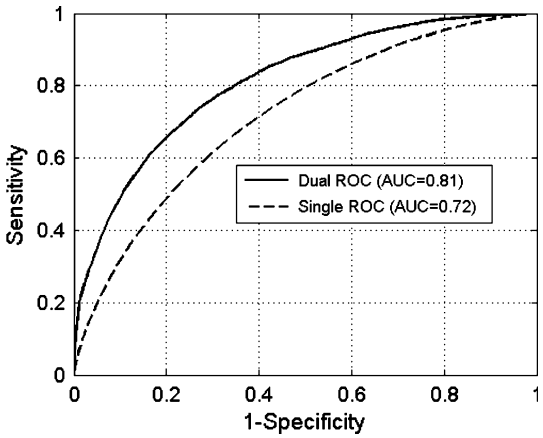

Fig. 9 The ROC curves for dual measurement of both fall rate and BMD (AUC = 0.81), and for single measurement of BMD only (AUC = 0.72)

The ROC curves for the single (BMD only) and dual measurement (BMD and fall rate) cases are shown in Fig. 9. As may be seen, the dual measurement case has better performance (AUC = 0.81) than the single measurement case (AUC = 0.72).

4 Discussion

This paper has presented a new stochastic model for quantifying hip fracture risk in individuals. The model utilizes a thinned Poisson process that itself is a Poisson process and allows the statistics of hip fractures to be evaluated. As compared with previous approaches (such as proportional hazards or logistic regressions), the model is mechanistic in that it incorporates explicitly falls and loads as random events and variables, respectively, as well as bone strength represented though DXA based estimates of bone mass. The model, because it is mechanistic, allows for a functional understanding of why, for example, there are many individuals with high bone mass who fracture while many with lower bone mass do not. An assumption that differences in bone quality over and above that as reflected in bone mass are required to explain this observation seems somewhat questionable in light of the results presented here. As also shown, the model can explain why the existence of a prior fracture can significantly increase the risk of future fracture. In particular, the model showed a 1.6-fold increase in fracture risk because of a prior fracture, which is similar to clinical data that demonstrates an increase of risk by a factor of two [11, 26, 29, 36].

It has previously been established that falls are an important risk factor for hip fracture. For example, Kaptoge et al. [32] has shown that falls are more predictive of hip fractures than BMD. However, it appears that it has not

yet been fully recognized how falls and BMD are quantitatively interconnected in terms of hip fracture prediction. In a related context, the World Health Organization's fracture risk estimation tool ("FRAX") does not incorporate an individual's likelihood of falling into the computation of hip fracture risk, stating as justification that consistent fall data was not available and that pharmaceutical intervention has not been shown to reduce fracture risk in patients selected on the basis of a fall history [30]. However, it has been shown that patients selected on the basis of risk factors for falling may respond less completely to agents that preserve bone mass than patients selected on the basis of low BMD [30]. In view of the present model, this finding may be explained by the fact that fall rates are not affected by bone drugs, and thus such patients may not show as great a response to therapy as expected. In addition, the expected decrease in hip fracture risk by, for example, therapeutic increase in BMD (or any factor by which the strength of a bone increases), as the present stochastic model demonstrates, is in fact dependent on fall rate, so that the expected benefit from therapy would also be fall-rate dependent (see (5)). Indeed, another useful feature of the proposed model is that it may enable researchers to determine how much improvement in the ability to predict hip fracture could be realized if better estimates of bone strength (i.e., over and above that provided by DXA-determined BMD) were able to be realized. For example, hip BMD has been shown to account for up to 88% of the observed variations in femoral strength, as determined in vitro [13]. The proposed model should be able to determine if the use of other bone factors (such as hip axis length, degree of mineralization, cortical thickness or trabecular architecture) that together with BMD might explain more of the observed variations in strength, could in fact significantly impact the estimates of hip fracture risk. This can be accomplished, for example, by including varying amounts of noise in the relationship between bone density and strength, (8), and using computer simulation techniques [56].

In a related context, the ROC analysis demonstrated that improvement in performance (as reflected in AUC, for example) can be achieved when knowledge of fall rate is included in the measurement space. However, the model and data presented also demonstrate that there is an upper bound on such performance. That is to say, even with perfect knowledge of bone density (strength) and of fall rate (the likelihood of a fall), there is far from ideal prediction of who will and who will not fracture. That this may be the *fundamental nature* of the fracture risk problem has not been fully appreciated by the osteoporosis research community.

A seminal study by Hui et al. [24] demonstrated that fracture risk was age and BMD dependent, with results that were very similar to the data generated by our model as in Fig. 4. They also utilized a Poisson model, but did so with an ad hoc analysis that did not mechanistically seek to statistically characterize the occurrence of hip fractures.

The model as presented here requires further development in order for it to become clinically useful. For example, methods should be developed in order to estimate an individual's fall rate, λ. Clearly relying solely on age is not optimal, and methods which incorporate as many factors as possible should be studied. Various tests (such as the ability to rise from a chair without the use of hands) could also be incorporated into the estimation of fall rate. Certainly, the prior history of falling would be one key aspect to include in the estimation procedure. One approach would be to model the fall rate, λ, distributed a priori as a gamma-distribution. Based on the number of falls observed a maximum a posteriori estimate of the fall rate could be made; more falls would lead to a higher estimate of fall rate. This and other Poisson-mixtures should be explored in the context of the presently proposed model.

It will also be necessary to develop additional insights on the probability distribution function for the load induced at the hip. The Weibull distribution function was chosen because of its simplicity and its ability to model a wide range of statistical phenomena. However, as more information on load statistics is developed, it may be helpful to use a different distribution. It may also be necessary to incorporate additional information into the load distribution parameters. For example, an age-based dependence on the parameters may be useful to reflect the fact that older individuals generally have less ability to compensate for a fall and will often sustain a higher induced load at the hip. Similarly, analysis as to how height and weight affect the induced load and how to incorporate this information into the distribution parameters should also be addressed. For example, as one extension to the Weibull model, a tri-modal probability distribution can be utilized, in which one mode models a fall to the side, another mode models a fall to the front, while a third mode models a fall to the back. The fall to the side could use as a mean load the peak force imparted to the hip in a sideways fall as reported in [54, 65], while a backwards or forward fall would be associated with lower mean peak forces, respectively. Additional details on load statistics could be garnered from other studies, such as those reporting on the "biomechanical fracture threshold" [22, 34]. This latter work, although developed in a deterministic context, could be incorporated into a more comprehensive specification of the load probability density function. Additional information on higher order (e.g., variance) load statistics would need to be determined by further studies.

Regardless of the probability distribution for the induced load at the hip, the thinned Poisson model can be adapted in a straightforward manner. With respect to the general question of how to estimate the thinned Poisson process model parameters, a maximum likelihood approach could be utilized [9, 66]. This will also enable the model to be validated based on empirical (clinical) data, which besides hip fracture statistics would also need to include fall data statistics.

It will also be of interest to see if the model can provide useful insights as to why bisphosphonates reduce the incidence of hip fractures without commensurate increases in BMD [17, 19, 52, 60]. For example, if patients in a particular clinical trial have associated with them a random load distribution that was clustered around their hip strengths, then small changes in strength (as caused for example by small changes in BMD and/or degree of bone mineralization) may result in large reductions in fracture risk. In a similar context, if a group of patients in a given trial have associated with them large fall rates, this can also serve to amplify the effect of treatment. This is because a sensitivity analysis using (4) shows that the sensitivity coefficient relating relative decrease in fracture risk to relative increase in bone strength is linearly proportional to fall rate, λ. Furthermore, although the strength of bone may be linearly related to BMD (for example as shown in [8] for a sideways fall in vitro), the conditional probability of fracture may have a higher (than one) power dependency on BMD that may arise out of the stochastic nature of the problem (see (7), for example). It will also be useful to see if the model can produce insights on the significant impact that vitamin D has on the occurrence of fractures. For example, it is known that vitamin D impacts calcium absorption (with the potential to maintain or improve bone density and bone strength) as well as muscle function (with the potential to decrease the likelihood of a fall) [5, 57]. The thinned process model shows that this would have a multiplicative effect through changes in both λ and p_S.

The model as presented can also be extended in several ways. For example, thinned Poisson process should be able to model fracture risk of the distal radius and humerus. However, the model does not appear to be suitable for vertebral fractures, as the latter are not typically associated with a fall. Also the model as proposed is time-invariant; however it can be extended to cases where the fall rate and conditional probability of fracture are time-dependent, using well-known methods associated with non-homogeneous Poisson processes [63]. This may, for example, be appropriate in long term predictions of fracture risk (e.g., over a period of 10 years), when a decade of life may be associated with significant changes in fall rate and/or conditional probability of fracture.

The stochastic model presented here for quantifying hip fracture risk is not intended as a replacement for proportional hazards or logistic regression models that have proved useful in a variety of clinical studies in evaluating risks associated with many factors. It also does not at all contradict that there are indeed other bone-specific factors besides bone mass that have an impact on bone strength. Rather, the primary purpose of the stochastic model presented is to elucidate the hypothesis that the hip fracture process is inherently random, and that better estimates of hip strength over and above that provided by DXA-BMD operate in a highly "noisy" environment, and may therefore have only modest ability to impact clinical practice. Indeed this result may have been presaged in a seminal paper by the pioneering statistician C. Frederick Mosteller, who in 1952 published a technical paper entitled "The World Series Competition" [46]. In this paper, Mosteller showed that the stronger team would often lose to a weaker team, simply because of chance. A substitution of words provides a characterization of the findings here: an individual having a stronger hip would often break while an individual having a weaker hip would not, *simply because of chance*.

In conclusion, a new stochastic model has been proposed that appears to capture the intrinsic aspects of the risk of hip fracture. The thinned Poisson process model characterizes the occurrence of falls as random events and induced loads at the hip as random variables, and uses a measure of strength (DXA-derived BMD) to model the key components associated with a hip fracture. The model provides estimates of hip fracture risk as a function of fall rate and DXA-derived BMD. Perhaps the most important aspect of the model is the exposition that the occurrence of a hip fracture is intrinsically stochastic, and that the ability to identify accurately who will and who will not fracture may be inherently limited.

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