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Intraoperative risk management of hyperparathyroidism: Modeling and testing the parathyroid hormone's evolution as a mean reverting stochastic processes

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ABSTRACT

This paper describes and validates a stochastic model (Ornstein–Uhlenbeck process) for parathyroid hormone (PTH) levels. Rapid intraoperative parathyroid hormone assay supports the emergence of a minimally invasive approach to unilateral parathyroid exploration in the surgical treatment of hyperparathyroidism. The model's goal is to verify whether a cure has been attained with excision of abnormal parathyroid tissue, based on intraoperative measurements, sparing the need for a bilateral exploration. The scarcity of PTH observations renders the classical methods of goodness-of-fit tests (GoFT) and cure criteria inadmissible or numerically challenging. The paper suggests a new approach to accomplish these goals given limited data. The GoFT strongly supports the model and consequently the induced cure criterion. This model will clarify the confusion in the literature regarding the required PTH decay representing a high likelihood of cure from hyperparathyroidism.

1. Introduction

Primary hyperparathyroidism represents a pathological condition where at least one of the normally four parathyroid glands hyper-secrete parathyroid hormone with multiple medical consequences including osteopenia, kidney stones and cardiovascular compromise. The recent advent of rapid intraoperative parathyroid hormone assay has facilitated minimally invasive surgery for hyperparathyroidism, whereby unilateral exploration for the insulting gland may suffice and replace the traditional 'gold standard' of bilateral, four-gland exploration. A significant intraoperative decay in the parathyroid hormone (**PTH**) level after the removal of an abnormal gland indicates that the offending parathyroid tissue has been removed, with a low likelihood of any remaining abnormal parathyroid tissue. Consequently, the need to explore the contralateral side and subject the patient to the inherent risks of bilateral explorations, including recurrent laryngeal nerve injury and postoperative hypocalcemia, are avoided.

The combination of the relatively short half-life of in-vivo PTH and rapid intraoperative PTH (**iPTH**) assay have led to the widespread use of this technique during parathyroidectomy. Once the offending parathyroid tissue is removed, the degree of iPTH decrease is used as a marker indicating a "cure". However, the success of this technique is critically dependent on an accurate criterion for a "significant" iPTH decrease, as an indicator that all abnormal parathyroid glands have been removed. Modeling the evolution of the PTH process and empirically verifying it, by a goodness-of-fit test (GoFT), is a prerequisite to its clinical application via the establishment of a cure criterion. These are therefore the main goals of this paper. Such a model, and its induced criterion, would clarify the existing confusion in the literature regarding the required PTH decay that would represent a high likelihood of cure from hyperparathyroidism.

Modeling the evolution of the PTH level is entrenched in the idea that there exists a "normal" equilibrium level of PTH. Once this equilibrium is impaired there are several physiological processes that attempt to return the PTH level back to normal. The evolution of the PTH level in the blood, due to this physiological process, is dynamic. At any given point in time the in-vivo PTH is being both degraded as a function of several variables including cardiac output, kidney function and metabolic rate, and being produced by the parathyroid gland based on a complex positive feedback of

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Calcium, Phosphate and Vitamin D levels. Therefore it is natural to assume that PTH levels are not constant, rather they fluctuate around a certain equilibrium level. Consequently, due to random changes of the influencing factors, the nature of the evolution of the PTH process is stochastic with a tendency to increase when it is below this equilibrium level and vice versa. Stochastic processes of this nature are called "mean reverting processes" (MRP), e.g., Uhlenbeck and Ornstein [1] (**OU**). MRP have been used in different fields to describe phenomena of this nature including Biology and Financial Economics among others. For a "soft" general introduction to these processes and their uses see Grimmet and Stirzaker [2].

Modeling PTH evolution was pioneered by Libutti et al. [3] and later extended by Bieglmayer, Prager and Niederle [4]: we refer to the extended model as the ELB model. These papers, however, assume a deterministic evolution which given the description above seems to be overly simplified and too rigid to capture the observed PTH evolution. Nevertheless, the basic mean reverting stochastic process is such that its expected value, as a function of time, coincides with this deterministic model. There are only a few, three of four, intraoperative iPTH observations per patient. The ELB model is implemented utilizing these limited observations to estimate both of its parameters and consequently the cure rule is judged.

Furthermore, PTH blood levels are investigated on symptomatic individuals and are not routinely tested in the otherwise healthy general population. Therefore, a long sequence of PTH data from healthy populations, in which every observation can be considered as coming from the OU limiting stationary distribution, is virtually nonexistent. This presents an obstacle for the implementation of the Cramer–von Mises standard GoFT in the literature. Moreover, the cure criteria and decision cannot be based on the limiting (asymptotic) distribution of a test statistic, as there are mostly only three or four iPTH observations to support this decision.

Regardless of the chosen model, the scarcity of observations presents an obstacle to the generation of a (statistically) reliable and significant decision rule. Our implementation of the stochastic approach overcomes, to a certain extent, this obstacle. Under the assumption of a MRP it is possible to utilize some information of the general (healthy) population for parameter estimation and devise a cure rule. Under the OU the parameters are implicit in the "normal bounds" of the healthy population. This method of parameter estimation is used routinely in financial economics; see Becker [5]. It alleviates the challenge of estimating parameters based on a scarcity of observations and gives rise to a 'cure rule' that could be based on a time-depended confidence interval. Since such a rule would not be based on a solitary cut-off point but an interval, it would still be reliable even for an individual patient.

The paper suggests and investigates a GoFT, albeit an indirect test, that unlike the Cramer–von Mises standard test can be implemented given the data limitation. The suggested test is a joint test, of the available data to the MRP with the implicit estimated parameters. While we are not aware of this test being used in the context of GoFT to the MRP, a similar idea has been used before in the context of models' risk and value at risk in financial economics; see Granger, White and Kamstra [6], Kupiec [7], Cont [8] and Christoffersen [9]. Similarly, the properties and scarcity of the iPTH observations make the intuitive cure criterion based on a standard confidence interval numerically cumbersome to use. Hence a variant of this criterion is suggested.

The remainder of the paper is organized as follows. Section 2 concisely explains the mean reverting process, followed by a section stipulating the difficulties in applying the standard GoFT to the available database and the need for a newly designed test. Section 4 suggests and executes an indirect GoFT that can be applied to the available database. In Section 5 a cure criterion is developed, empirically illustrated and compared to the ELB model. Conclusions are offered in the final section.

2. Modeling the PTH's evolution and estimating its parameters

The MRP fits the random nature of the PTH evolution process. An MRP can incorporate the tendency to gravitate to a long-term equilibrium level. Thus when the PTH is above the normal level, the process has a decreasing trend and vice versa. Mean reverting stochastic processes are common across many areas of science. The OU diffusion is the basic model of this type and is used here.

The characteristics of the OU process fit the reality of the PTH stochastic evolution.

Immediately after removing a pathologic parathyroid gland the PTH level is high and a new equilibrium, with a lower value, is in the process of being reached. In the course of reaching equilibrium, the PTH level decreases (exponentially) until the process is stabilized (with random fluctuations) around the new lower equilibrium value. Given the dynamic environment affecting PTH decay and production, especially in the operative setting, it is reasonable to assume that the PTH level is random and is described by the OU process, as motivated in the introduction above.

The PTH process is continuous in nature and changes occur at every instant. It is represented by the stochastic differential equation

$$ds = k(r - s)dt + \sigma dz \tag{1}$$

where
r is the long term equilibrium "normal" level of the PTH,
dz is a standard Brownian motion, and
σ and k are positive constants.

The heuristic meaning of Eq. (1) is as follows: ds represents the incremental change in the PTH value over the "next instant" (over dt). The right hand side of (1) specifies the incremental change as composed of two parts: a deterministic part that equals k times $(r - s)dt$ and a stochastic part, σdz. Therefore if the realization of s is above r, the deterministic part of the increment will be negative and vice versa. The stochastic part, roughly speaking, can be described as σ times a random variable with an expected value of zero and a "very small" standard deviation ($\sqrt{dt}$). Hence, the expected value of the increment equals the deterministic part which reverts the process toward its long term normal level of r.

The implication of (1) (derived by integration) about the distribution of $S(t)$ given $S(0)$ conveys more accurately the "mean reverting" property. Over an interval $[0, t]$ given $S(0) = s_0$ and assuming the OU process, the value of the PTH at time t, represented by $[S(t)|S(0) = s_0]$, is a normal random variable with a variance of

$$Var\left[S(t)|S(0) = s_0\right] = \frac{\sigma^2}{2k}\left(1 - e^{-2kt}\right) \tag{2}$$

and an expected value of

$$E\left[S(t)|S(0) = s_0\right] = r + (s_0 - r)\, e^{-kt}. \tag{3}$$

Hence, when $r < s_0$ ($r > s_0$) the realized PTH value at time 0 is above (below) r and $s_0 - r$, the deviation of the PTH value from its long run is positive (negative). Thus, as long as $k > 0$, the expected value of the PTH at time t will be closer to its long run value r, as the expected deviation $(s_0 - r)\, e^{-kt}$ is a fraction of the realized deviation. Thus $S(t)$, in expected value, reverts to the long run mean.

In fact, the right hand side of Eq. (3) concisely describes the ELB deterministic model. Therefore, when $k > 0$, the ELB is a model of an exponential decay. Furthermore, k is the exponential decay rate of the expected value of the continuous evolution process of the PTH.

Eqs. (2) and (3) also describe the general relation between the expected value and the variance of $S(t_{i+1})$ given $S(t_i) = s_{t_i}$ when t is replaced with $t_{i+1} - t_i$ and s_0 with s_{t_i}.