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Stochastic Analysis of Noncompliance with Drug Therapy

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Abstract

When it comes to drugs, a major concern may stem from drug noncompliance [5]. Patient medication compliance is a key factor for the efficacy of any therapy. This paper addresses issues from stochastic analysis of Markov processes for modeling irregular (or variable) compliance settings. The major questions addressed in [2] are associated with the mean and variance of the drug concentration; we suggest that a hybrid stochastic differential system could improve the study established there. To the best of our knowledge, such modeling is quiet novel as regards pharmacokinetics and pharmacodynamics.

Keywords: drug therapy, compliance, pharmacodynamics, stochastic analysis

1 Introduction

The effectiveness of drug treatment in clinical practice is considerably lower than the efficacy shown in controlled studies. A major factor contributing to the lower effectiveness of drug treatment is noncompliance. There are several factors influencing compliance including drug type and formulation, disease status, health care system, community care and family. But compliance is more closely dependent on patient individual behavior. Patient questionnaires allow the identification of some profiles of non-compliers, here we consider that variable compliance stem from the age (non-compliers are usually younger [3]) and the treatment duration: most of the patients rely on their memory to ensure that they are taking their medication correctly. But the phenomenon is repetitive for years and usually under the same conditions, so that memory could be defective (e.g. noncompliance may start the first year and increase thereafter).

Compiling drug dosing history data turns patients' variable adherence from a source of confusion to a source of knowledge. Here the question of how much credibility one has in patient questionnaires must be addressed first. Since 1986, AARDEX has developed products to measure and analyze patient adherence to prescribed drug dosing regimens in both trials and practice. Patient's drug intakes are electronically monitored by Medication Event Monitoring Systems (MEMS®). The MEMS monitors are drug packages with integral electronic micro circuitry designed to compile the dosing histories of ambulatory patients' prescribed medications [4]. MEMS readers transfer dosing-history data from MEMS monitors to a MS-Windows-based computer. The main benefit of well documented, detailed, and reliable dosing history data is a more accurate and cost-effective analysis of collected clinical data.

1.1 Multi-dosing with Full Compliance: Drug Concentration Response for Intravenous Administration

The drug is administered in multiple fixed doses $\{d_i\}_{i=1,2...}$ at some well determined instants $\{t_i\}_{i=1,2...}$. Here we assume instantaneous inputs of the drug into the systemic concentration. It is well accepted that kinetics of first order are involved in the elimination process. The following is a single-compartment pharmacokinetic model with elimination coefficient $k_e > 0$,

$$\begin{aligned} \dot{x}(t) &= -k_e\, x(t) \quad t \in [t_{i-1}, t_i[\\ x(t_i) &= x(t_i^-) + d_i \end{aligned}$$

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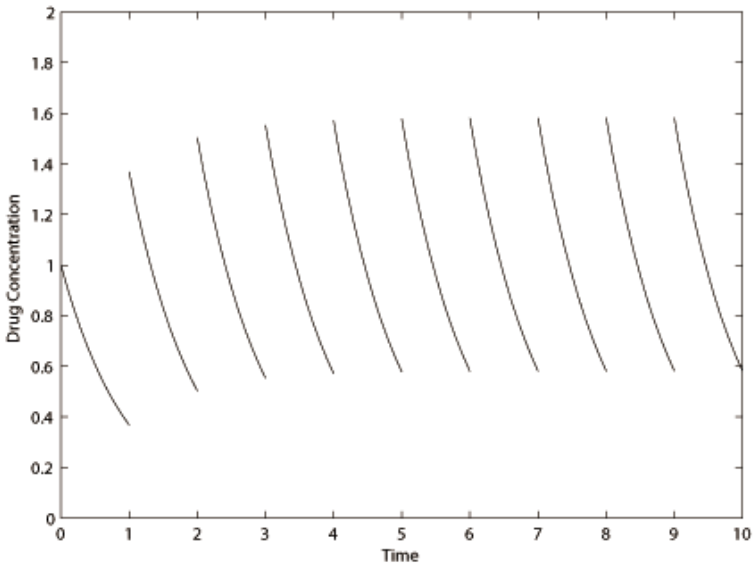
$x(t)$ denotes the drug concentration; it is plotted in the following figure for a particular prescribed drug regimen.



However, either of the regimen components may vary: the duration between consecutive administration times and the dose value. Now the administrations are given at increasing random times $\{T_i\}_{i=1,2...}$ and the corresponding doses $\{D_i\}_{i=1,2...}$ are random variables as well. A possible approach towards this problem, thus, can only be stochastic modeling. The following in Section 2 is the proposed model. It is a hybrid stochastic differential system, described in general first and then applied to study the drug concentration response to multi-dosing intravenous administration when the compliance is variable.

2 A Hybrid Stochastic Differential System: PDP

Roughly speaking, a piecewise deterministic process (PDP) is a mixture of a deterministic motion and random jumps of two kinds, spontaneous and predictable ones. The state space of a PDP is a disjoint union of some manifolds with boundary. Some vector field determines the motion between jumps. The jump mechanism has two further ingredients: a hazard rate for spontaneous jump times and a probability measure to reinitiate the motion after any jump, of both types, so that the deterministic motion starts afresh after every random jump. This results in a càdlàg stochastic process which is strong Markovian. The vector field, the jump rate and the transition measure are the triplet of ingredients also called local characteristics of a PDP. This process has been widely used since Davis introduced it in 1984. The reference [1] is our main tool on the subject.

State space E **:** a disjoint union

$$E = \{\xi = (x, y) \,:\, y \in Y,\, x \in M_y\} \triangleq \bigcup_{y \in Y} M_y$$

where Y is a discrete set either finite or countable. For each $y \in Y$, M_y is an open set from $\mathbb{R}^{d(y)}$, here d is a function on Y into $\mathbb{N}$.

Thus, a PDP is denoted (x_t, y_t) or ξ_t with $t \in \mathbb{R}_+$; y_t is a Y-valued continuous-time process and x_t is a continuous-time process with values in M_y as long as $y_t = y$. y_t is said the discrete component of the state and x_t its continuous or phase component.

Vector field Φ **:**

$$y_0 = y \in Y \quad x_0 = x \in M_y$$
$$x_t = c(t) \quad t \in [0, T_1[$$

$c(t)$ is the integral curve (or flow) of a vector field Φ at x, that is a map such that

$$c(0) = x \quad \dot{c}(t) = \Phi\left(c(t)\right).$$

(Recall that T_1 is the instant of the first jump of x_t.)

Jumping rate λ **:** T_1 is a random variable with the following probability distribution

$$\mathbb{P}_\xi\left\{T_1 > t | \mathcal{F}_t\right\} = \exp\left(-\int_0^t \lambda(\xi_s)\, ds\right) \quad t \in [0, t_{\rm b}(\xi)[$$

where $t_{\rm b}(\xi) = t_{\rm b}(x, y)$ is the instant at which the curve c starting at x reaches the boundary ∂M_y ; $t_{\rm b}(\xi) = +\infty$ if this never occurs.

We define the active (or essential) boundary Γ as a set of boundary points $\bar{\xi} = (\bar{x}, \bar{y})$ of the state space such that

$$\lim_{x \to \bar{x}} \mathbb{P}_{\xi=(x,\bar{y})}\left\{T_1 = t_{\rm b}(\xi) < \infty\right\} = 1.$$

These are boundary points almost surely reachable by the process within a predictable time, where it jumps instantaneously.

Transition measure $\mathbf{Q}$ **:** the conditional probability distribution under $\mathbb{P}_{\xi=(x,y)}$ of the post jump state $\xi(T_1)$ given the conditioning event

$$\left\{\xi(T_1^-) = (\bar{x}, y)\right\}$$

for $(\bar{x}, y) \in E \cup \Gamma$. This is the probability under $\mathbb{P}_{(x,y)}$ of transition from $x(T_1^-) = \bar{x}$ and $y(T_1^-) = y$ to the set $d\xi' \in \mathcal{E}$ ($\mathcal{E}$ is the Borel σ-algebra of E), i.e.

$$\mathbf{Q}(\bar{x}, y, d\xi') = \mathbb{P}_{(x,y)}\left\{\, (x(T_1), y(T_1)) \in d\xi' \,|\, x(T_1^-) = \bar{x}\,,\, y(T_1^-) = y\right\}.$$

2.1 Back to the Application in Subsection 1.1

First of all we set these assumptions:

- $\{D_i\}_{i=1,2\ldots}$ is a sequence of positive random variables which are mutually independent and identically distributed;
- $\{T_i\}_{i=1,2\ldots}$ and $\{D_i\}_{i=1,2\ldots}$ are independent.

It is clear that the above model can be applied for drug concentration when compliance is variable; the remainder now is to identify all its ingredients. Here the discrete component has only one possible value, i.e., Y is a singleton $\{y\}$. Thus, we omit to denote any dependence on y in the following. $M =]0, +\infty[$, $\Phi(x) = -k_{\rm e}\, x$, and $c(t) = x \exp(-k_{\rm e} t)$. $\partial M = \{0\}$ and $t_{\rm b}(x) = +\infty$ for all x, this is because ∂M is never reached and thus the essential boundary $\Gamma = \emptyset$.

As to actuarial analysis, we assume only two sorts of patients: sick and undergoing a therapy, or dead. Let t_0 be the person's age when he/she falls sick, this is his/her age on starting the therapy as well; t_0 is assumed known. Let t be the time elapsed since the therapy was taken up, this is also the current sickness duration. A sick person dies at a random time with hazard rate $\lambda_{\rm d}$ depending on its age and the sickness duration. When a patient dies, the therapy finishes. Besides, we assume a fixed finite period $t_{\rm f}$ for the therapy. Then $t \in [0, t_{\rm f}]$, and for $t = t_{\rm f}$ the therapy finishes as well. The phase component x_t of the process represents the drug concentration and jumps with rate $\lambda_{\rm c}(t_0 + t, t)$ depending on the current patient's age and therapy duration. This is in link with what is announced in the very beginning of the introduction. Then the total hazard rate of jumping is $\lambda(t_0 + t, t) = \lambda_{\rm d}(t_0 + t, t) + \lambda_{\rm c}(t_0 + t, t)$, and after every jump the process either sticks at a life-after-death Δ with probability $\lambda_{\rm d}/\lambda$ or is reinitiated according to

$$\mathbf{Q}(\bar{x}, dx') = \mathbb{P}_x\left\{\, x(T_i) \in dx' \,|\, x(T_i^-) = \bar{x}\right\}$$

with probability λ_c/λ. As to the Markov kernel $\mathbf{Q}$ we recall that

$$x(T_i) = x(T_i^-) + D_i \quad i = 1, 2, ...$$

Here we need the common probability distribution to the D_i's. This calls for statistical characterization of the sequence $\{D_i\}_{i=1,2...}$. The dose distribution is either discrete with finite support (e.g. for solid dosage), or a distribution with density on a bounded interval from $]0, +\infty[$. In any case, this is the typical statement of the theory of large samples in classical mathematical statistics, i.e., statistics of independent identically distributed observations $\{D_1, ..., D_n\}$ in the asymptotics $n \to \infty$. Since drug dosing history data are not available, let us take as example a uniform distribution for the random doses.

3 The PDP Differential Formula

This section gives the key to compute expectations for PDP's. This formula is in fact a corollary of the calculus establishing the extended generator for a PDP (see pages 69-74 of [1]).

Theorem 1 *Let $\xi_t = (x_t, y_t)$ be a PDP with state space E and essential boundary Γ. Let f be a measurable function $f : E \cup \Gamma \to \mathbb{R}$ such that: for each $\xi = (x, y) \in E$ the map $t \to f[c(t, x), y]$ is absolutely continuous on $[0, t_b(\xi)]$ (on $\mathbb{R}_+$ if $t_b(\xi)$ is not finite). Then for each $t \geq 0$,*

$$f(\xi_t) - f(\xi_0) = \int_0^t \mathfrak{U}f(\xi_s)\, ds + \sum_{i\geq 1} \mathbb{1}_{\{0 < T_i \leq t\}}\, \mathbb{1}_{\{\xi_{T_i^-} \in \Gamma\}}\, \mathfrak{C}f(\xi_{T_i^-}) - \int_0^t \int_E [f(\xi_{s-}) - f(\xi')]\, q(ds \times d\xi'). \tag{1}$$

Notation The operator $\mathfrak{U}$ is given by

$$\mathfrak{U}f(\xi) = \Phi f(\xi) + \lambda(\xi) \left\{ \int_E f(\xi')\mathbf{Q}(\xi, d\xi') - f(\xi) \right\} \quad \xi \in E$$

where

$$\Phi f(\xi) = \Phi f(x, y) = \sum_{i=1}^{d(y)} \frac{\partial f}{\partial x^i}(\xi)\Phi^i(x),$$

$\mathfrak{U}$ is called the extended generator of ξ_t. The operator $\mathfrak{C}$ is given by

$$\mathfrak{C}f(\xi) = \int_E f(\xi')\mathbf{Q}(\xi, d\xi') - f(\xi) \quad \xi \in \Gamma.$$

Remark. Associated to the process ξ_t, $q(ds \times d\xi')$ is a compensated random measure counting jumps to $d\xi'$ at jump instants in ds. The stochastic integral

$$\int_0^t \int_E [f(\xi_{s-}) - f(\xi')]\, q(ds \times d\xi')$$

in formula (1) is a martingale if for any starting point $\xi \in E$ and each $t \geq 0$,

$$\mathbb{E}_\xi \left\{ \sum_{i\geq 1} \mathbb{1}_{\{0 < T_i \leq t\}} |f(\xi_{T_i}) - f(\xi_{T_i^-})| \right\} < \infty.$$

This holds in particular if f is bounded and if for any starting point $\xi \in E$ and each $t \geq 0$,

$$\mathbb{E}_\xi \left\{ \sum_{i\geq 1} \mathbb{1}_{\{0 < T_i \leq t\}} \right\} < \infty.$$

3.1 The Application (continued)

We claim that the operators $\mathfrak{U}$ and $\mathfrak{C}$ involved in the differential formula for our process are given by: for $t < t_{\rm f}$ and $x \in]0, +\infty[$,

$$\mathfrak{U}f(t,x) = \frac{\partial f}{\partial t}(t,x) - k_{\rm e}\, x \frac{\partial f}{\partial x}(t,x) - \lambda(t_0+t,t) f(t,x) +$$

$$\lambda_{\rm d}(t_0+t,t) f(\Delta) + \lambda_{\rm c}(t_0+t,t) \int_{x' \in]0,+\infty[} \mathbf{Q}(x, dx') f(t,x')$$

and

$$\mathfrak{C}f(t_{\rm f}, x) = f(\Delta) - f(t_{\rm f}, x)$$

for $x \in]0, +\infty[$. Since the main thing is the drug concentration response so long as the therapy doesn't stop, there is no loss of information in setting this convention: we extend functions at Δ by 0. Then

$$\mathfrak{U}f(t,x) = \frac{\partial f}{\partial t}(t,x) - k_{\rm e}\, x \frac{\partial f}{\partial x}(t,x) - \lambda(t_0+t,t) f(t,x) +$$

$$\lambda_{\rm c}(t_0+t,t) \int_{x' \in]0,+\infty[} \mathbf{Q}(x, dx') f(t,x') \quad t < t_{\rm f} \quad x \in]0, +\infty[,$$

$$\mathfrak{C}f(t_{\rm f}, x) = -f(t_{\rm f}, x) \quad x \in]0, +\infty[.$$

In addition, if the process jumps to Δ, it stays there, this says that $\mathbf{Q}(\{\Delta\}, \bullet) = 0$. Since by convention $f(\Delta) = 0$, $\Phi(\Delta) = 0$ and $\lambda(\Delta) = 0$, then

$$\mathfrak{U}f(\Delta) = 0.$$

Now we are ready to write the differential formula for our process: *Let f be a measurable function $f : [0, t_f] \times]0, +\infty[\cup \{\Delta\} \to \mathbb{R}$ such that for each $x \in]0, +\infty[$, the map $t \to f\left(t, x \exp(-k_e t)\right)$ is absolutely continuous on $[0, t_f]$. Then for each $t < t_f$,*

$$f(t, x_t) - f(0, x_0) = \int_0^t \left\{ \frac{\partial f}{\partial s}(s, x_s) - k_e\, x_s \frac{\partial f}{\partial x}(s, x_s) - \lambda(t_0+s, s) f(s, x_s) \right.$$

$$\left. + \lambda_c(t_0+s, s) \int_{x' \in]0,+\infty[} \mathbf{Q}(x_s, dx') f(s, x') \right\} ds$$

$$- \int_0^t \int_{[0,t_f] \times]0,+\infty[\cup \{\Delta\}} \left[f(s, x_{s-}) - f(\xi') \right] q(ds \times d\xi').$$

We must have

$$f(t_f, x(t_f^-)) = f(\Delta) = 0.$$

Under the condition of the Remark, and by the optional stopping theorem we obtain the Dynkin formula for our process. This condition holds naturally in our application; it just says that the mean number of administrations per finite time interval is finite. The Dynkin formula is the main tool for calculating expectations for a wide class of functions.

Dynkin's formula: For each $t < t_{\rm f}$,

$$\mathbb{E}_x \left\{ f(t, x_t) \right\} - f(0, x) = \mathbb{E}_x \left\{ \int_0^t \left[\frac{\partial f}{\partial s}(s, x_s) - k_{\rm e}\, x_s \frac{\partial f}{\partial x}(s, x_s) - \right. \right.$$

$$\left. \left. \lambda(t_0+s, s) f(s, x_s) + \lambda_{\rm c}(t_0+s, s) \int_{x' \in]0,+\infty[} \mathbf{Q}(x_s, dx') f(s, x') \right] ds \right\}.$$

Now we are able to show how the mean and the variance of the drug concentration evolve in time by applying the Dynkin formula to both $f(x) = x$ and $f(x) = x^2$. Denote $\mathbf{p}$ the common distribution density to the doses

$$\mathbf{p}(x) = \frac{1}{D_{\max}} \mathbb{1}_{]0, D_{\max}]}(x).$$

The following is the derivation of an ordinary differential equation for the drug concentration mean $\mathbb{E}_\mu \{x_t\}$ denoted $m(t)$. The notation $\mathbb{E}_\mu$ means expectation under $\mathbb{P}_\mu$; this is equivalent to say that x_t starts at $t = 0$ with probability law μ. In fact, for any probability distribution μ on $]0, +\infty[$, we define a probability measure on Ω by

$$\mathbb{P}_\mu\{\bullet\} = \int_{x \in]0,+\infty[} \mathbb{P}_x\{\bullet\} \mu(dx),$$

μ is nothing but the probability distribution of x_0 under $\mathbb{P}_\mu$. For each $t < t_{\mathrm{f}}$,

$$\begin{aligned}
m(t) &= m(0) + \int_0^t \left[-k_{\mathrm{e}} - \lambda(t_0 + s, s)\right] m(s) ds + \\
&\quad \mathbb{E}_\mu \left\{ \int_0^t \lambda_{\mathrm{c}}(t_0 + s, s) \int_{x' \in]0,+\infty[} \mathbf{p}(x' - x_s) x' \, dx' \, ds \right\} \\
&= m(0) + \int_0^t \left[-k_{\mathrm{e}} - \lambda(t_0 + s, s)\right] m(s) ds + \\
&\quad \mathbb{E}_\mu \left\{ \frac{1}{D_{\max}} \int_0^t \lambda_{\mathrm{c}}(t_0 + s, s) \int_{x' \in]x_s, x_s + D_{\max}]} x' \, dx' \, ds \right\} \\
&= m(0) + \int_0^t \left[-k_{\mathrm{e}} - \lambda(t_0 + s, s) + \lambda_{\mathrm{c}}(t_0 + s, s)\right] m(s) ds + \frac{D_{\max}}{2} \int_0^t \lambda_{\mathrm{c}}(t_0 + s, s) \, ds \\
&= m(0) + \int_0^t \left[-k_{\mathrm{e}} - \lambda_{\mathrm{d}}(t_0 + s, s)\right] m(s) ds + \frac{D_{\max}}{2} \int_0^t \lambda_{\mathrm{c}}(t_0 + s, s) \, ds.
\end{aligned}$$

This is equivalent to

$$\frac{dm(t)}{dt} = \frac{D_{\max}}{2} \lambda_{\mathrm{c}}(t_0 + t, t) - \left[k_{\mathrm{e}} + \lambda_{\mathrm{d}}(t_0 + t, t)\right] m(t) \quad t \in [0, t_{\mathrm{f}}[. \tag{2}$$

Similar calculation gives an ODE for the second order moment $\mathbb{E}_\mu \left\{(x_t)^2\right\}$ denoted $m_2(t)$:

$$\begin{aligned}
\frac{dm_2(t)}{dt} &= \frac{D_{\max}^2}{3} \lambda_{\mathrm{c}}(t_0 + t, t) - \left[2k_{\mathrm{e}} + \lambda_{\mathrm{d}}(t_0 + t, t)\right] m_2(t) + \\
&\quad D_{\max} \lambda_{\mathrm{c}}(t_0 + t, t) m(t) \quad t \in [0, t_{\mathrm{f}}[.
\end{aligned} \tag{3}$$

Solving equation (2) first and then equation (3) with the initial conditions below gives the variance of the drug concentration

$$m(0) = \int_{]0,+\infty[} \mu(dx) x, \quad m_2(0) = \int_{]0,+\infty[} \mu(dx) x^2.$$

4 Conclusion and Future Work

Compliance with medical recommendations, especially with drug therapy is a complex challenge. We give an advance in the understanding of variable compliance using tools from stochastic analysis of jumping Markov processes, in the light of the seminal work of M.H.A. Davis.

A big open question remains about $\lambda(t_0 + t, t)$: how to construct estimators for this jumping intensity? It is surprising that statistical inference based on a PDP model has received little attention in the literature despite the wide range of applicability of such a model. Here the observations are the jump times $\{T_i\}_{i=1,2...}$ related to λ via the generalized exponential distribution.

In a near-future work we hope to be able to model the drug concentration response to oral-instead of intravenous-multi-dosing with variable compliance. In this case, we presume that the resulting process is nothing but a two-dimensional PDP.

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References

[1] Davis, M.H.A., *Markov Models and Optimization*, Chapman & Hall, 1993.

[2] Li, J., and F. Nekka, A pharmacokinetic formalism explicitly integrating the patient drug compliance, *Journal of Pharmacokinetics and Pharmacodynamics*, vol.34, no.1, pp.115–139, 2006.

[3] Meyers, K.E., P.D. Thomson, and H. Weiland, Noncompliance in children and adolescents after renal transplantation, *Transplantation*, vol.62, pp.186–189, 1996.

[4] Urquhart, J., The electronic medication event monitor: lessons for pharmacotherapy, *Clinical Pharmacokinetics*, vol.32, no.5, pp.345–356, 1997.

[5] Wuerzner, K., C. Hassler, and M. Burnier, Difficult blood pressure control: watch out for noncompliance, *Nephrology Dialysis Transplantation*, vol.18, pp.1969–1973, 2003.