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Markov Chains for Random Urinalysis III: Daily Model and Drug Kinetics

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James P. Boyle

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This is the third in a series of reports on the use of Markov chains for the analysis of random urinalysis programs. A Markov model for random drug urinalysis testing that allows for daily variations in testing probabilities was developed. The formulation allows for any fixed length cycle (e.g., week, month). Drug kinetics and drug user gaming are incorporated into the Markov model via conditional probabilities. The Markov chain provides estimates of the distribution of time to detection and mean time to detection. The analyses have shown that time to detection varies dramatically with varying (observed) daily testing rates. Unequal daily testing rates provide opportunities for gaming drug users to extend the mean time to detection. Gaming is not possible with equal probabilities of testing across days.

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Foreword

This report was prepared as part of the Statistical Methods for Drug Testing project (Program Element 0305889N, Work Unit 0305889N.R2143DR001), sponsored by the Chief of Naval Personnel (PERS-63). The objective of the project is to develop a unified set of statistical methodologies for the analysis of drug testing programs and data. The work described here was performed during FY93.

This is the third in a series of reports on the use of Markov chains for the analysis of random urinalysis programs. The first report is *Markov Chains for Random Urinalysis I: Age-Test Model* (NPRDC-TN-93-5). The second report is *Markov Chains for Random Urinalysis II: Age-Test Model With Absorbing State* (NPRDC-TN-93-6). Related work also includes *Probability of Detection of Drug Users by Random Urinalysis in the U.S. Navy* (NPRDC-TN-93-2).

We thank Cecil Hornbeck from the San Diego Navy Drug Screening Laboratory for the use of his data.

MURRAY W. ROWE
Director, Manpower Systems Department

Summary

Background

Since 1981, the U.S. Navy has maintained a *zero tolerance* drug policy. The cornorstone of this policy is an aggressive urinalysis testing program. The testing program is intended to deter and detect drug abuse, as well as provide data on the prevalence of drug abuse.

Previous work (Thompson, Boyle, & Hentschel, 1993; Boyle, Hentschel, & Thompson, 1993) developed Markov models for analyzing random urinalysis strategies stratified by "time last tested" (i.e., age-test strategies). This report describes a method to quantify the effects of daily variations in random urinalysis testing rates on detection of drug users. The report, an extension of Thompson and Boyle (1993), presents a daily Markov model that includes drug excretion rate kinetics.

Objective

The objective of this work is to quantify the effects of daily variations in random urinalysis testing rates on detection of drug users.

Approach

First, daily drug testing is modeled as a Markov chain. This chain includes parameters for daily drug testing probabilities and for conditional probabilities of testing positive. Second, a model for the conditional probabilities of testing positive for cocaine use is presented. Drug dosage is treated as a random variable and its distribution is developed using Navy data. Third, times to detection for various drug testing and drug usage patterns are compared using the above models.

Results

Analyses of four examples of weekly testing patterns are presented. The first two examples represent the observed random sampling behavior of two Navy activities. The third example shows equal testing rates on weekdays and no testing on weekends. The fourth example is equal testing rates every day of the week. All of the examples have been standardized to a 15% monthly testing rate.

In each example, once per week cocaine use is assumed. The average time to detection for the first activity varies from 12.7 to 409.7 months depending on the day of the week cocaine is used. For the second activity, average time to detection varies from 12.2 to 106.5 months. If an activity does not test on weekends, a Friday night user averages 271.1 months to detection. Average time to detection under constant rate daily testing is 27.3 months.

Conclusions

A Markov model for random drug urinalysis testing that allows for daily variations in testing probabilities was developed. The formulation allows for any fixed length cycle (e.g., week, month). Drug kinetics and drug user gaming can be incorporated into the Markov model via conditional

probabilities. The Markov chain provides estimates of the distribution of time to detection and mean time to detection.

The cocaine kinetics model presented here provides the probability of testing positive as a function of time since ingestion. Initial dose is treated as a random variable and the distribution of initial dose is estimated from Navy data.

The analyses have shown that time to detection varies dramatically with varying (observed) daily testing rates. Unequal daily testing rates provide opportunities for gaming drug users to extend the mean time to detection. Gaming is not possible with equal probabilities of testing across days.

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Introduction

Since 1981, the U.S. Navy has maintained a *zero tolerance* drug policy. The cornerstone of this policy is an aggressive urinalysis testing program. [illegible] ing program is intended to deter and detect drug abuse, as well as provide data on the prevalence of drug abuse. All officer and enlisted personnel are subject to random urinalysis testing on a continuing basis. Current policy (Chief of Naval Operations [CNO], 1990) directs Navy commands to test 10 to 20% of their members each month. The Navy's random urinalysis program has been successful in reducing the proportion of service members testing positive for drugs (7% in 1983 compared to 1% in 1991). However, since any drug abuse impacts readiness, health, and safety, continuous evaluation and improvement of the Navy's program is required.

Previous reports (Thompson, Boyle, & Hentschel, 1993; Boyle, Hentschel, & Thompson 1993) developed Markov models for analyzing random urinalysis strategies stratified by "time last tested" (i.e., age-test strategies). In related work, Evanovich (1985) uses Markov chains to model the probability of detection of drug users. Stoloff (1985) investigates the relationship between deterrence and random urinalysis testing.

This report describes a method to quantify the effects of daily variations in random urinalysis testing rates on detection of drug users. The report, an extension of Thompson and Boyle (1992), presents a daily Markov model that includes drug excretion rate kinetics. The Markov models allow for a fixed length daily cycle (e.g., weekly, monthly) and include an absorbing state for detection. Drug-specific urinary excretion rates are also modeled. Initial drug dose is treated as a random variable. Optimal gaming strategies, using data from the current Navy urinalysis program, are then developed. These strategies treat initial drug dose as a random variable. Finally, the report presents the survival distributions of time to detection under optimal gaming and under constant testing rates.

A relevant issue, not previously addressed, is drug detection time in urine. The detection times vary by drug. For example, marijuana is detectable for approximately 2 to 4 days, cocaine for approximately 1 to 2 days, and methamphetamine for approximately 2 to 3 days. Detection times also vary by dose, analytical test method used, individuals physical condition, fluid intake, and method and frequency of ingestion. Discussions of urinary excretion kinetics of cocaine, marijuana, methamphetamines, and amphetamines appear in Ambre, Ruo, Nelson, and Belknap (1988); Beckett and Rowland (1965); Hamilton, et al. (1977); Johansson, Gillespie, and Halldin (1990); Johansson and Halldin (1989); and Cook, et al. (1992).

Existence of drug user gaming can be gleaned from the Department of Defense surveys of substance abuse and health behavior among military personnel. Five surveys have been conducted since 1980. The most recent was the 1992 Worldwide Survey (Bray, et al., 1992). These surveys provide comprehensive and detailed estimates of the prevalence of drug use among military personnel. Results from the 1992 Worldwide Survey show that 55.9% of drug users believe "drug users curtail use when they think they will be selected for urinalysis." About 6.6% of surveyed Navy personnel admitted to some drug use in the past 12 months. This indicates a need for random urinalysis programs that are not predictable or programs that drugs users do not believe are predictable. As a result, drug user gaming strategies are investigated here.

The Daily Model

Using the theory and notation developed in previous reports (Thompson, et al., 1993; Boyle, et al.,1993), a class of Markov chains with transition matrices, P, of the following form can be defined:

$$P = \begin{bmatrix} 0 & 1-\alpha_1 p_1 & 0 & 0 & \cdots & 0 & \alpha_1 p_1 \\ 0 & 0 & 1-\alpha_2 p_2 & 0 & \cdots & 0 & \alpha_2 p_2 \\ \cdot & \cdot & \cdot & \cdot & & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & & \cdot & \cdot \\ 0 & 0 & 0 & 0 & \cdots & 1-\alpha_{d-1}p_{d-1} & \alpha_{d-1}p_{d-1} \\ 1-\alpha_d p_d & 0 & 0 & 0 & \cdots & 0 & \alpha_d p_d \\ 0 & 0 & 0 & 0 & \cdots & 0 & 1 \end{bmatrix} . \quad (1)$$

Given that an individual is in state i, p_i is the probability of the individual being tested and α_i is the conditional probability of a positive result. Note that an individual is in state i ($2 \leq i \leq d$) if an individual was in state i - 1 one time period earlier and either was not tested or tested negative. An individual is in state 1 if an individual was in state d one time period earlier and either was not tested or tested negative. State $d + 1$ is the single absorbing state. An individual is in state $d + 1$ (detected) if tested positive. For the applications in this report, a fixed length daily cycle of $d = 7$ is assumed. Here states 1 to 7 represent Sunday through Saturday, respectively.

The p_i's and α_i's are allowed to be unrestricted probabilities. That is, $0 \leq p_i \leq 1$ and $0 \leq \alpha_i \leq 1$, $\forall i$. However, $\alpha_i p_i \neq 0$ for at least one i. This constraint guarantees that states 1 through d are transient and, starting in any transient state, an individual must be caught in finite time with certainty.

With the above assumption and a theorem in Taylor and Karlin (1984), the matrix P from Equation 1 can be written as:

$$P = \begin{bmatrix} Q & R \\ O & I \end{bmatrix}$$

with

$$Q = \begin{bmatrix} 0 & 1-\alpha_1 p_1 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 1-\alpha_2 p_2 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 1-\alpha_3 p_3 & \cdots & 0 \\ \cdot & \cdot & \cdot & \cdot & & \cdot \\ \cdot & \cdot & \cdot & \cdot & & \cdot \\ \cdot & \cdot & \cdot & \cdot & & \cdot \\ 0 & 0 & 0 & 0 & \cdots & 1-\alpha_{d-1}p_{d-1} \\ 1-\alpha_d p_d & 0 & 0 & 0 & \cdots & 0 \end{bmatrix}$$

and I - Q nonsingular. Recalling that the matrix

$$W = (I - Q)^{-1}$$

is the fundamental matrix, some standard results needed in the next section can be stated. First, the following notation is employed:

W_{ij} is the ijth element of W,

T is time to detection or absorption by state $d + 1$,

P^n_{ij} is the ijth element of P^n, and

X_n is the state of the process at time n.

Using these definitions and theory from Taylor and Karlin (1984):

$$P\left[T \leq n \mid X_0 = i\right] = P^n_{i\,d+1},$$

$$E\left[T \mid X_0 = i\right] = \sum_{j=1}^{d} W_{ij} = \tau_i,$$

and

$$\left\{ VAR\left[T \mid X_0 = i\right] \right\} = (2W - I)\,\tau - \tau_{SQ}$$

for $i = 1, \ldots, d$. τ_{SQ} is the elementwise square of τ. If the row vector Π_0 is any initial distribution for the process concentrated on the transient states, the above implies

$$P\left[T \leq n\right] = \sum_{i=1}^{d} \Pi_0(i)\, P^n_{i\,d+1}$$

and the unconditional distribution function of T can be computed. Its expectation and variance are

$$E\left[T\right] = \Pi_0 \tau$$

and

$$VAR\left[T\right] = \Pi_0 (2W - I)\,\tau - (\Pi_0 \tau)_{SQ}.$$

Finally, for an individual, the number of tests Y over d time periods has mean and variance

$$E\left[Y\right] = \sum_{i=1}^{d} p_i$$

$$VAR\left[Y\right] = \sum_{i=1}^{d} p_i(1 - p_i).$$

Drug Kinetics

Gibaldi and Perrier (1982) characterize drug elimination from the body after rapid intravenous injection as following first-order kinetics. Specifically, the rate of loss of the drug from the body is given by

$$\frac{dX}{dt} = -kX(t) \tag{2}$$

where $X(t)$ is the amount of drug in the body at time t after injection. The constant k is called the apparent first order elimination rate. Equation 2 is a first order linear differential equation and is easily solved to yield

$$X(t) = x_0 e^{-kt}$$

where x_0 is the amount of drug ingested (i.e., the initial dose).

Additionally, some of the drug is excreted unchanged in the urine (i.e., renal excretion) and again by first-order kinetics the rate of appearance of intact drug in the urine is proportional to the amount of drug in the body. Thus,

$$\frac{dX_u}{dt} = k_e X(t) = k_e x_0 e^{-kt} \tag{3}$$

where $X_u(t)$ is the cumulative amount of drug excreted in the urine to time t and k_e is the apparent first-order rate constant for renal excretion. Integrating Equation 3 yields

$$X_u(t) = \frac{k_e x_0}{k}(1 - e^{-kt}). \tag{4}$$

Note that $\lim_{t \to \infty} X_u(t) = k_e x_0/k$ and k_e/k represents the fraction of the initial dose eliminated unchanged in the urine.

Drug elimination from the body through metabolism also follows first-order kinetics with

$$\frac{dM}{dt} = k_f X(t) - k_m M(t) \tag{5}$$

where $M(t)$ is the amount of metabolite in the body at time t. The constants k_f and k_m are the respective apparent first-order rate constants for metabolite formation and elimination. Equation 5 is linear and by elementary methods can be solved to yield

$$M(t) = \frac{k_f x_0}{k - k_m} \left[e^{-k_m t} - e^{-kt} \right] . \tag{6}$$

The differential equation describing the appearance of metabolite in the urine is

$$\frac{dM_u}{dt} = k_{mu} M(t) \tag{7}$$

where $M_u(t)$ is the amount of metabolite in the urine and k_{mu} is the apparent first-order rate constant for the excretion of metabolite in the urine. Using Equations 6 and 7 yields the time rate of change of metabolite in the urine as

$$\frac{dM_u}{dt} = \frac{k_{mu} k_f x_0}{k - k_m} \left[e^{-k_m t} - e^{-kt} \right] . \tag{8}$$

Ambre (1985) subjected previously published urinary excretion data on cocaine and its metabolites to kinetic analysis using the first-order models described above. He obtained the following parameter estimates for cocaine (COC) and its metabolite benzoylecgonine (BZ):

$$\begin{aligned} k &= 0.464 \\ k_e / k &= 0.03 \\ k_f &= 0.2134 \\ k_m = k_{mu} &= 0.0923. \end{aligned}$$

These values can be used in Equations 3 and 8 yielding time paths of change in milligrams per hour. Ambre also assumed a urination rate of 1 milliliter per minute. Thus, concentrations in nanograms per milliliter are obtained through multiplication of Equations 3 and 8 by the factor $1000^2/60$. The resulting expressions are

$$\begin{aligned} Y_{COC}(t) &= \frac{1000^2 (.03)(.464)}{60} x_0 e^{-.464t} \\ &= 232 x_0 e^{-.464t} \end{aligned} \tag{9}$$

$$\begin{aligned} Y_{BZ}(t) &= \frac{1000^2 (.0923)(.2134)}{60 (.464 - .0923)} x_0 \left[e^{-.0923t} - e^{-.464t} \right] \\ &= 883.1863 x_0 \left[e^{-.0923t} - e^{-.464t} \right] \end{aligned} \tag{10}$$

where $Y_{COC}(t)$ and $Y_{BZ}(t)$ are respectively urine concentrations for COC and BZ in nanograms per milliliter (ng/ml) at t hours after ingestion of a dose x_0 in milligrams (mg) of cocaine. To illustrate, Figure 1 is a semilogarithmic plot (converted to logs base 10) of concentration curves for dose levels of 50 and 100 milligrams of cocaine.

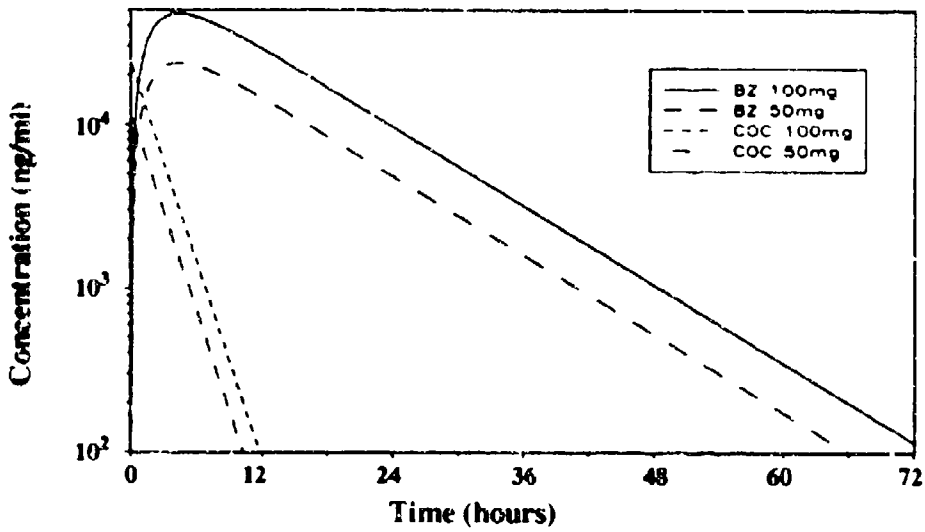

Figure 1. Concentrations of cocaine and benzoylecgonine in urine versus time from ingestion.

Concentrations of cocaine and benzoylecgonine for 1,076 urinalysis tests were obtained from the San Diego Navy Drug Screening Laboratory. This represents all the specimens that tested positive for BZ and had detectable amounts of COC over a 2-year period. Figure 2 is a scatter plot of BZ concentration versus COC concentration on these paired values.

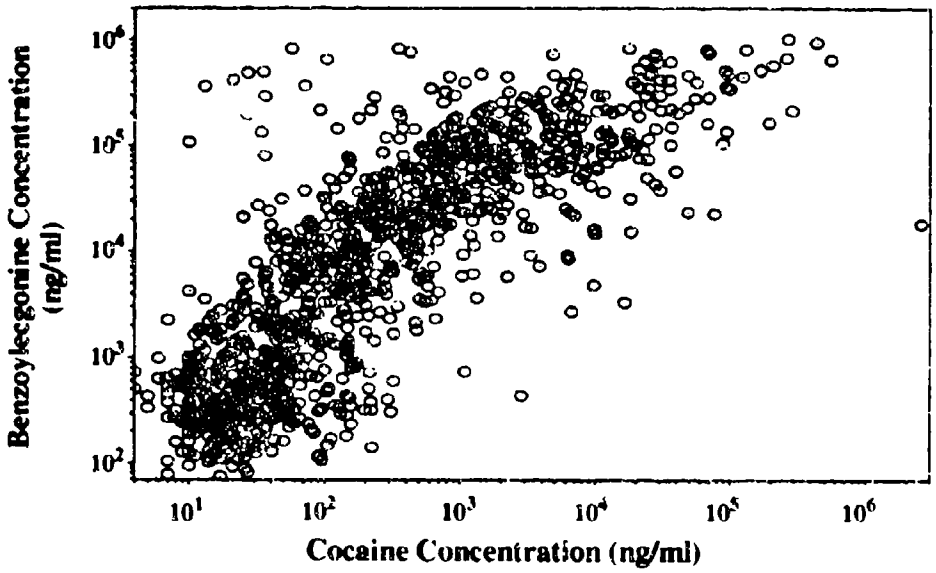

Figure 2. Scatter plot of benzoylecgonine concentration versus cocaine concentration in urine.

Equations 9 and 10 can be solved for the initial dose x_0 and the time since ingestion t by taking natural logs and simplifying. The resulting two linear equations in two unknowns in matrix form are

$$\begin{bmatrix} 1 & -.464 \\ 1 & -.0923 \end{bmatrix} \begin{bmatrix} \ln x_0 \\ t \end{bmatrix} = \begin{bmatrix} \ln\left[Y_{COC} / 232\right] \\ \ln\left[(883.1863 Y_{COC} + 232 Y_{BZ}) / (232 \cdot 883.1863)\right] \end{bmatrix} .$$

Solving the above equations for each of the 1,076 observations yields a distribution on initial dose x_0. Figure 3 is a frequency distribution of $\log_{10} x_0$ in milligrams.

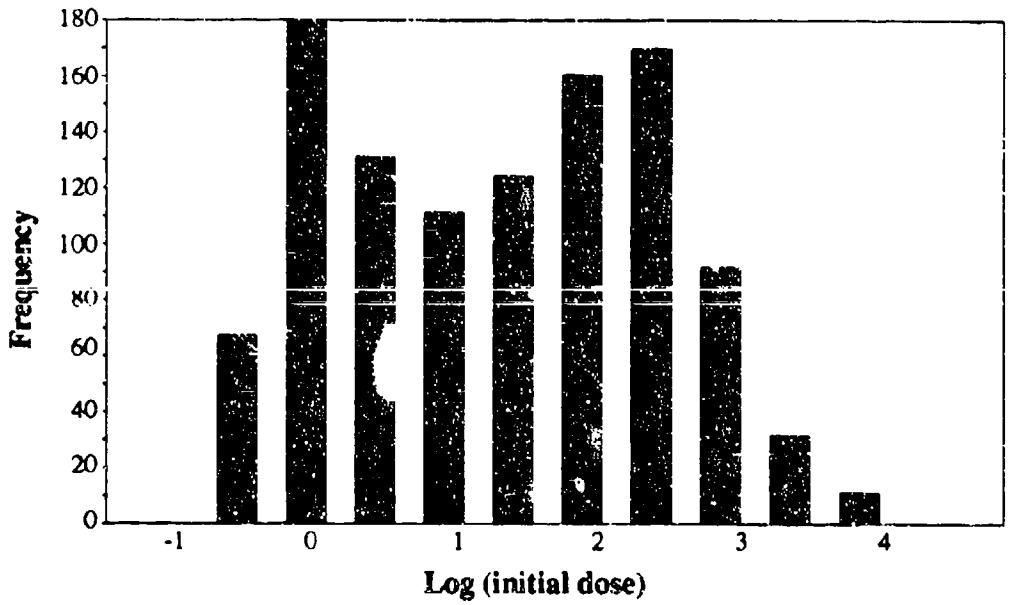

Figure 3. Frequency distribution of $\log_{10}$ initial dose in milligrams.

The probabilities of testing positive can now be determined from the distribution of initial dose x_0. At any time t after ingestion, the probability of testing positive is

$$\begin{aligned} \alpha(t) &= P\left[Y_{BZ}(t) \geq 150 \text{ ng/ml}\right] \\ &= \frac{\#\text{ of } x_0 \text{ values with } Y_{BZ}(t) \geq 150}{1076} . \end{aligned}$$

The probabilities of testing positive for values $t = 12, 36, 60, \ldots, 156$ hours were computed. These times correspond to 1 to 7 days, assuming drug ingestion at 10:00 p.m. and testing at 10:00 a.m. each day. Table 1 lists the probabilities.

Table 1

Probabilities of Testing Positive for Cocaine Use 1 to 7 Days After Ingestion

Day	t (hours)	$\alpha(t)$
1	12	.9376
2	36	.6508
3	60	.1229
4	84	0
5	108	0
6	132	0
7	156	0

Applications

Analyses of four examples of weekly testing patterns are presented in this section. The first two examples (UIC A AND UIC B) represent the observed random sampling behavior of two Navy activities. The results are averaged over a 2-year period. The third example shows equal testing rates on weekdays and no testing on weekends. The fourth example is equal testing rates every day of the week. All of the examples have been standardized to a 15% monthly testing rate, or a 3.5% weekly testing rate ($7 / 30 \cdot 0.15 = 0.035$). A monthly rate of 15% represents the midpoint of the mandated (CNO, 1990) Navy range of monthly rates (10 to 20%).

Table 2 contains the weekly random sampling testing pattern, the probability of being tested, and the mean time to detection by day of week for UIC A. The first line of values in the table (Percentage of Tests) is the observed testing pattern expressed as the percentage of tests conducted by day of week. The second line (Probability Tested) is the probability of being tested standardized to a 0.035 weekly testing rate. The third line (Average Detection Time [months]) is the average time to detection assuming cocaine is used once a week and on the same day of the week each week. UIC A does almost all of its testing on Saturday, Sunday, and Monday. If cocaine is used every week on Friday night, the average time to detection is 12.7 months. If cocaine is used every week on Saturday night the average time to detection is 13.3 months. Compare this to cocaine use on Monday night where the average time to detection is 409.7 months or 34 years. While the UIC A strategy catches the weekend users, it allows gaming drug users to significantly increase time to detection.

Table 2

Daily Model for Random Sample Testing and Cocaine Use (UIC A)

	Day of the Week						
	Sun	Mon	Tue	Wed	Thu	Fri	Sat
Percentage of Tests	29.4	34.5	0	2.5	0	2.5	31.1
Probability Tested	.0103	.0121	0	.0009	0	.0009	.0109
Average Detection Time (months)	20.3	409.7	251.4	122.3	25.4	12.7	13.3

Another example of an observed Navy testing pattern is shown in Table 3. This activity does half of its testing on Fridays. The best strategy for a once a week cocaine user at this command is to use on Sunday with an average detection time of 106.5 months or 8.9 years. Table 4 shows the effects of not testing on weekends. Cocaine could be used once a week on Friday with a 271. month average time to detection. Table 5 shows the average time to detection when the daily testing rate is constant across day of week. Regardless of when the drug user ingests cocaine average time to detection is 27.3 months.

Table 3

Daily Model for Random Sample Testing and Cocaine Use (UIC B)

	Day of the Week						
	Sun	Mon	Tue	Wed	Thu	Fri	Sat
Percentage of Tests	8.8	0	7.1	13.3	11.5	50.5	8.8
Probability Tested	.0031	0	.0025	.0047	.0040	.0177	.0031
Average Detection Time (months)	106.5	39.8	25.5	14.9	12.2	47.7	73.0

Table 4

Daily Model for Random Sample Testing and Cocaine Use (Constant Testing on Weekdays)

	Day of the Week						
	Sun	Mon	Tue	Wed	Thu	Fri	Sat
Percentage of Tests	0	20	20	20	20	20	0
Probability Tested	0	.007	.007	.007	.007	.007	0
Average Detection Time (months)	19.4	19.4	19.4	20.9	35.5	271.1	43.0

Table 5

Daily Model for Random Sample Testing and Cocaine Use (Constant Testing on Everyday)

	Day of the Week						
	Sun	Mon	Tue	Wed	Thu	Fri	Sat
Percentage of Tests	14.3	14.3	14.3	14.3	14.3	14.3	14.3
Probability Tested	.005	.005	.005	.005	.005	.005	.005
Average Detection Time (months)	27.3	27.3	27.3	27.3	27.3	27.3	27.3

Conclusions

A Markov model for random drug urinalysis testing that allows for daily variations in testing probabilities was developed. For example, if a command does not test on weekends, this model can be used to investigate the effect. Although the examples presented here are weekly models, the formulation allows for any fixed length cycle (e.g., month). Drug kinetics can be incorporated into the Markov model via conditional probabilities. The conditional probabilities of testing positive given that an individual is tested are included as model parameters. Also, drug user gaming strategies can be included via these conditional probabilities. The Markov chain provides estimates of the distribution of time to detection and mean time to detection.

The cocaine kinetics model presented here provides the probability of testing positive as a function of time since ingestion. Initial dose is treated as a random variable and the distribution of initial dose is estimated from Navy data. Models for other drugs could be developed from the literature cited earlier.

The analyses have shown that time to detection varies dramatically with varying (observed) daily testing rates. Unequal daily testing rates provide opportunities for gaming drug users to extend the mean time to detection. Gaming is not possible with equal probabilities of testing across days.

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