

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 August 2009 (20.08.2009)

PCT

(10) International Publication Number
WO 2009/102474 A2

(51) International Patent Classification:
A61B 5/20 (2006.01) *G01N 33/15* (2006.01)
G06F 17/11 (2006.01)

(21) International Application Number:
PCT/US2009/000925

(22) International Filing Date:
13 February 2009 (13.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/028,640 14 February 2008 (14.02.2008) US

(71) Applicant (for all designated States except US): **THE UNIVERSITY OF MIAMI** [US/US]; 1600 N.W. 10th Avenue, Miami, FL 33136 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **AFSHARTOUS, David, R.** [US/US]; Jackson Towers, 15th Floor West, 1500 N.W. 12th Avenue, Miami, FL 33136 (US). **PRESTON, Richard, A.** [US/US]; Jackson Towers, 15th Floor West, 1500 N.W. 12th Avenue, Miami, FL 33136 (US).

(74) Agent: **BOUTSIKARIS, Leonidas**; Nixon & Vanderhye P.C., 901 North Glebe Road, 11th Floor, Arlington, VA 22203-1808 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: RECURSIVE ESTIMATION METHOD AND SYSTEM FOR PREDICTING RESIDUAL BLADDER URINE VOLUMES

(57) Abstract: The Recursive Residual Estimation method and system are used to estimate the residual bladder volumes via a mathematical model of the bladder process. Regardless of the substance of primary interest, the method utilizes conservation of mass and conservation of concentration principles relative to a substance of secondary interest in order to solve a system of recursive equations. The method only requires the specification of two initial values: the initial residual volume and the creatinine mass introduced per unit time into the bladder.



WO 2009/102474 A2

- 1 -

RECURSIVE ESTIMATION METHOD AND SYSTEM FOR PREDICTING RESIDUAL BLADDER URINE VOLUMES

CROSS-REFERENCES TO RELATED APPLICATION

[0001] This application claims priority to U.S. Application 61/028,640, filed February 14, 2008, the entire contents of which are incorporated herein by reference.

FIELD OF THE TECHNOLOGY

[0002] The technology herein relates to a method and a system for estimating residual bladder volumes of urine not emptied during voiding. More particularly, a mathematical model of the bladder process is used to solve a system of recursive equations to predict the residual volumes at each time point. The algorithm relies on conservation of mass and conservation of concentration principles using production of referenced substance that is known to be produced in the human body at constant rate.

BACKGROUND AND SUMMARY

[0003] Clinical research studies often collect data via repeated measurements of collected urine. Such measurements are collected over fixed time intervals and analyzed as a function of time. Timed urine collections are inexpensive, noninvasive, relatively simple to conduct, and can provide valuable data on kidney function and the clearance of various electrolytes and drugs by the kidney.

[0004] For example, early clinical testing of new drugs often involves measuring the amount of drug excreted by the kidney in a timed urine collection. This data is critical to understanding and documenting the elimination of a drug by the kidney. Quantitative elimination of a drug by the kidney (as opposed to hepatic metabolism) is key clinical pharmacology data that is essential for drug development. Collection of repeated urine volumes is also key in clinical studies of renal physiology. For example, renal elimination of potassium, a critical physiological process, can be quantitatively studied by administering a standard potassium load followed by hourly determination of urinary potassium (see, for

example, [1] Preston R.A. et al., "Comparative effects on renal potassium excretion of candesartan versus lisinopril in hypertensive patients with type II diabetes mellitus", *J. Clin. Pharmacology*, 2002; 42:754-761, [2] Perez G.O. et al., "Blunted kaliuresis after an acute potassium load in patients with chronic renal failure", *Kidney Intern.*, 1983; 24:656-62, [3] Perez G.O. et al., "Potassium homeostasis in chronic diabetes mellitus", *Arch. Intern. Med.* 1977; 137:1018-22, [4] Smoller S. et al., "Blunted kaliuresis after an acute oral potassium load in diabetes mellitus", *American Journal of the Medical Sciences*, 1988; 295:114-21, [5] Perez G.O. and Oster J.R., "Aldosterone responsiveness to an acute potassium load in diabetes mellitus and chronic renal insufficiency", *Hormone Research*, 1987; 27(1):30-5, [6] Oster J.R., "Renal response to potassium loading in Sickle Cell Trait", *Arch. Intern. Med.*, 1980; 140:534-36, [7] Fernandez J. et al., "Impaired extrarenal disposal of an acute oral potassium load in patients with end stage renal disease on chronic hemodialysis", *Mineral & Electrolyte Metabolism*, 1986; 12:125-9).

[0005] Unfortunately, the accuracy of timed urine collections is limited by the presence of a residual volume of urine remaining in the bladder following each timed void due to incomplete emptying of the bladder of a patient. The existence of a residual volume of urine at each collection point presents difficulties when attempting to estimate the actual amount of a substance cleared by the kidney during the specified time interval. The residual urine volume adds significant imprecision to urine calculation methods, leaving a clinical research tool subject to inaccuracies. For example, the drug collected during a one hour urine collection may not represent the actual drug introduced into the bladder during that hour. Furthermore, the residual bladder volume may vary from one timed period to the next, and may actually increase when urine volumes are large and urine is collected frequently at short intervals.

[0006] A non-invasive method for determining bladder residual volumes is mentioned in U.S. Patent 6,770,295 by Kreilgard et al. where it is disclosed that mean residual volumes are measured by ultrasonic methods. Gerber et al. (US 2006/0020225) discloses a method for monitoring urodynamic information, including urine volume in the bladder, by using a monitor implanted in the bladder to wirelessly transmit information about the residual volume of urine following a voiding event.

[0007] The exemplary illustrative non-limiting technology herein addresses the above-described problems (e.g., imprecision and inaccuracies in urine collection methods) by

- 3 -

providing an unbiased method for estimating residual bladder volumes via a mathematical model for the residual bladder process.

[0008] One aspect of an exemplary illustrative non-limiting implementation relates to using a basic physical model to derive an equation for the total bladder volume at a given time point. Conservation of mass and conservation of concentration principles may be employed to derive an expression for the residual volume at any given time. By incorporating these principles towards a substance of secondary interest (e.g., creatinine, which the body produces at a relatively constant mass per unit time under steady state conditions), estimation of the residual volumes may be achieved.

[0009] The exemplary illustrative non-limiting modeling process incorporates quantities such as the new urine volume introduced into the bladder each time period, the urine volume voided each time period, the residual urine volume remaining after voiding, and their corresponding concentrations of electrolytes or drugs cleared by renal excretion. A recursive set of equations for the residual volumes is derived. These equations may be expressed in a Markovian fashion, so that the residual volume during a given time may be expressed in terms of the residual volume in the previous time period, and ultimately in terms of the residual volume during the initial time period and a series of model coefficients, which can also be solved recursively. The exemplary illustrative non-limiting algorithm computes the residual volumes solely from initial values for the residual volume and the creatinine parameter for each patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Fig. 1 is a schematic diagram of a residual volume of urine in the bladder of a patient predicted in accordance with an exemplary embodiment.

[0011] Fig. 2 is a schematic diagram of a physical model of the voiding process of the bladder in accordance with an exemplary embodiment.

[0012] Fig. 3 is a schematic diagram of a physical model of the voiding process for a simulated patient.

[0013] Fig. 4 shows the mean absolute deviation for the estimated values of r_1 and γ for the simulated patient of Fig. 3.

[0014] Fig. 5 shows feasible regions for values for r_1 and γ for the simulated patient of Fig. 3.

[0015] Fig. 6 illustrates an example system for calculating an estimate of the residual value of urine in the bladder of a patient in accordance to an exemplary embodiment.

DETAILED DESCRIPTION

1. Bladder Model

[0016] Fig. 1 schematically depicts a residual volume 12 of urine contained in the bladder 14 of a patient 10. The bladder 14 is connected to a kidney 16. Fig 2 shows in schematic form a physical model of the bladder voiding process used in an exemplary embodiment. At the start of a given time interval, for example, $t = 1$, the bladder contains a residual volume r_1 that was not emptied during voiding. Volume N_2 is introduced into the bladder during the next time interval. Hence, exactly at time $t = 2$ (right before voiding), the total volume in the bladder is $B_2 = N_2 + r_1$. Subsequently, after voiding, at time $t = 2 + \varepsilon$, a volume of urine C_2 is collected.

[0017] From the model of Fig. 2, it is seen that the total volume at the end of the time interval (just before voiding) is equal to the sum of the volume that will be voided plus the volume that will be leftover. Thus

$$B_t = N_t + r_{t-1} = C_t + r_t \quad (1)$$

or, in terms of the residual volume:

$$r_t = B_t - C_t = (N_t + r_{t-1}) - C_t \quad (2)$$

Since the amount of urine volume collected, C_t , is known, the residual volumes r_t can be found if the total bladder volume B_t at the end of each time interval is known.

[0018] In the exemplary illustrative non-limiting method presented herein, conservation of mass and conservation of concentration principles may be employed to derive mathematical expressions for B_t . Incorporation of these two principles in conjunction with a substance of secondary interest, for example, creatinine, results in the estimation of the residual volumes, r_t , which in turn allows one to accurately describe the behavior of a substance of primary interest, for example, potassium.

[0019] Specifically, it is assumed that the mass of creatinine produced by the body during each interval is substantially constant, say equal to γ . Then conservation of mass

- 5 -

implies that the mass of creatinine that exists in the volume B_{t+1} is equal to the mass leftover in r_t plus the new mass γ introduced during the time period. More formally,

$$Mass_{B_{t+1}} = Mass_{r_t} + \gamma. \quad (3)$$

Since the mass is equal to the concentration (in creatinine) times the volume,

$$Conc_{B_{t+1}} \times B_{t+1} = (Conc_{r_t} \times r_t) + \gamma \quad (4)$$

Solving for B_{t+1} ,

$$B_{t+1} = \frac{(Conc_{r_t} \times r_t) + \gamma}{Conc_{B_{t+1}}} = \frac{(Conc_{C_t} \times r_t) + \gamma}{Conc_{C_{t+1}}} \quad (5)$$

The last equation results from the observation that concentration of the collected urine is equal to that of the bladder volume just before collection.

[0020] Solving for the amount of new volume, N_{t+1} ,

$$N_{t+1} = \frac{(Conc_{C_t} \times r_t) + \gamma}{Conc_{C_{t+1}}} - r_t \quad (6)$$

[0021] Substituting equation (5) into equation (2), a single recursive equation requiring only initial values of r_1 and γ may be obtained:

$$r_t = \frac{(Conc_{C_{t-1}} \times r_{t-1}) + \gamma}{Conc_{C_t}} - C_t \quad (7)$$

[0022] Equation (7) is a recursive equation, representative of a Markovian system. The value of the parameter of interest, i.e., r_t , may then be expressed in terms of the initial value of the parameter. After some algebra, one obtains:

$$r_t = \left(\frac{Conc_{C_1}}{Conc_{C_t}} \right) r_1 + \left(\frac{t-1}{Conc_{C_t}} \right) \gamma - \left[\left(\sum_{i=2, t>2}^{i=t-1} \frac{Conc_{C_i} \times C_i}{Conc_{C_t}} \right) + C_t \right] \quad (8)$$

[0023] Equation (8) indicates that the recursive process is linear and it may be expressed as

$$r_t = a_{t1} r_1 + a_{t2} \gamma + a_{t3} \quad (9)$$

[0024] In the exemplary illustrative non-limiting embodiment presented herein, the coefficients of the recursive equation (9) are recursive themselves (for example, by inspecting equation (8)). Hence, a general algorithm to compute the residual volumes of urine for each patient only from initial values for r_1 and γ is provided.

- 6 -

1.1 Recursive Residual Estimation (RRE) Algorithm

An RRE algorithm includes the following four steps;

1. Specify an initial value for γ
2. Specify an initial value for r_1
3. Calculate the coefficients for r_2 and then calculate r_2 :

$$(a) \quad a_{21} = \frac{Conc_{C_1}}{Conc_{C_2}}$$

$$(b) \quad a_{22} = \frac{1}{Conc_{C_2}}$$

$$(c) \quad a_{23} = -C_2$$

$$(d) \quad r_2 = a_{21}r_1 + a_{22}\gamma + a_{23}$$

4. Recursively calculate the coefficients for r_{t+1} and then calculate r_{t+1} , for $t \geq 2$:

$$(a) \quad a_{(t+1)1} = a_{t1} \frac{Conc_{C_t}}{Conc_{C_{t+1}}}$$

$$(b) \quad a_{(t+1)2} = a_{t2} \frac{Conc_{C_t}}{Conc_{C_{t+1}}} + \frac{1}{Conc_{C_{t+1}}}$$

$$(c) \quad a_{(t+1)3} = a_{t3} \frac{Conc_{C_t}}{Conc_{C_{t+1}}} - C_{t+1}$$

$$(d) \quad r_{t+1} = a_{(t+1)1}r_1 + a_{(t+1)2}\gamma + a_{(t+1)3}$$

[0025] In an exemplary illustrative non-limiting embodiment presented herein, the basic model may be extended to describe a varying propensity to empty the bladder. For example, it may be that for some patients, a large residual is always immediately followed by a very small residual. This can be explained by the fact that a large residual stimulates a higher likelihood of emptying the bladder during the next period, whereas for other individuals the stimulus may take longer. However, it is found that the current model may capture this behavior without the explicit additional complexity. In other words, regardless of an individual's bladder emptying propensity, the only measurements needed to fully predict the residual behavior are the collected measurements and the r_1 and γ parameters.

2. Results-Sensitivity Analysis

[0026] The exemplary illustrative prediction model presented herein cannot be directly verified without observing actual residual volumes. However, in most cases this would require

actually placing a catheter or a monitor directly into the bladder. Bladder catheterization is invasive, and can potentially introduce infection. Hence, in order to verify the prediction model, several patients were simulated under a typical repeated measurements clinical trial design, where six hourly measurements are taken for each patient, measuring variables such as voided volume and creatinine concentration. Table 1 illustrates one of these patients.

Table 1: Simulated Patient

Variable	Hour					
	1	2	3	4	5	6
Voided volume (cc)	390	270	380	250	310	370
Actual residual (cc)	20	50	70	20	10	40
Voided concentration (mg/cc)	.10	.13	.11	.18	.14	.10

[0027] This patient was simulated based on a value of $\gamma = 41.6$ milligrams and a value of a first residual $r_1 = 20$ cc. These values reflect typical values for a “normal” patient. The value for γ was chosen by assuming a daily creatinine production of 1000 milligrams and assuming substantially constant excretion during the 24 hours. Since the values for the separate variables cannot be simulated independently, a stepwise process emulating the physical model of Fig. 2 was employed. The simulation requires the specification of the volume entering the bladder during each hour and both the residual volume and its corresponding concentration carried into the baseline hour. This process is shown in Fig. 3. Only the time points corresponding to immediately after voiding are shown to avoid crowding the diagram (corresponding to the $t + \varepsilon$ points in Fig. 2).

[0028] The potential bias in the observed measurements due to the existence of residual volumes can be seen by the above simulated data. For example, if the amount of the hourly creatinine is of interest, then the observed measurements can be misleading. Consider the change of creatinine from hour 1 to hour 2. Based on the observed measurements, there is a decrease in the amount of creatinine from 39 mg ($390 \text{ cc} \times .10 \text{ mg/cc}$) to 35.1 mg ($270 \text{ cc} \times .13 \text{ mg/cc}$). In other words, even though by design the creatinine production of the patient is constant each hour, a 10% decrease is predicted. Such discrepancies are common whenever there is variation in the residual and voided volumes.

[0029] Given estimates of the residuals, one may estimate the amount cleared of any substance of primary interest for a given time period by multiplying the new volume

introduced during the time period by its concentration. The new volume is collected volume, adjusted accordingly relative to the current and previous residual. In other words,

$$New\ Vol_t = C_t + r_t - r_{t-1}$$

However, the new concentration of the primary substance is not equal to the concentration of the collected volume ($Conc_t$), since the collected volume (C_t) is affected by the concentration of the previous residual. After some algebra, and utilizing the fact that the collected concentration is a weighted sum of the new volume concentration and the previous residual concentration, the desired concentration is derived:

$$New\ Vol\ Conc_t = \left(Conc_t - \frac{r_{t-1}}{C_t + r_t} Conc_{t-1} \right) \left(\frac{C_t + r_t}{New\ Vol_t} \right)$$

[0030] The RRE method and all subsequent coding and analysis was implemented using the statistical software R (see R-Project (2007), R-Version 2.2.1, website r-project.org). As expected, the method predicts residuals exactly if γ and r_1 are correctly specified. However, in actual practice, γ and r_1 are unknown and will have to be estimated. Since these are the only two values that need to be specified for estimating all the residual volumes r_t from the collected data, it is illustrative of the effectiveness of the exemplary model presented herein to access the robustness of the model to departures of the above two parameters from the real γ and r_1 values.

[0031] The robustness of γ and r_1 was investigated by considering different initial values for γ and r_1 , where said two parameters were under-specified and/or over-specified. For, example, incremental changes of 20% below and above the actual value in r_1 , and incremental changes of 5% below and above the actual value in γ were considered. The robustness of the model was evaluated by determining the mean absolute deviation of the real residuals from the estimated residuals. Table 2 contains the results for the simulated patient described above. Fig. 4 illustrates the results via an interpolated smooth surface.

Table 2: M.A.D. - Mean Absolute Deviation

γ	r_1										
	0	4	8	12	16	20	24	28	32	36	40
31.2	262.2	259.0	255.8	252.6	249.3	246.1	242.9	239.7	236.5	233.3	230.0
33.2	213.0	209.8	206.5	203.3	200.1	196.9	193.7	190.5	187.2	184.0	180.8
35.3	163.7	160.5	157.3	154.1	150.9	147.7	144.4	141.2	138.0	134.8	131.6
37.4	114.5	111.3	108.1	104.9	101.6	98.4	95.2	92.0	88.8	85.5	82.3
39.5	65.3	62.1	58.8	55.6	52.4	49.2	46.0	42.8	39.5	36.3	33.1
41.6	16.0	12.8	9.6	6.4	3.2	0.0	3.2	6.4	9.6	12.8	16.0
43.6	33.1	36.3	39.5	42.8	46.0	49.2	52.4	55.6	58.8	62.1	65.3
45.7	82.3	85.5	88.8	92.0	95.2	98.4	101.6	104.9	108.1	111.3	114.5
47.8	131.6	134.8	138.0	141.2	144.4	147.7	150.9	154.1	157.3	160.5	163.7
49.9	180.8	184.0	187.2	190.5	193.7	196.9	200.1	203.3	206.5	209.8	213.0
52.0	230.0	233.3	236.5	239.7	242.9	246.1	249.3	252.6	255.8	259.0	262.2

[0032] The zero value for the mean absolute deviation in the middle of Table 2 corresponds to the case where the values for γ and r_1 are exactly known. It can be seen from Table 2 that the exemplary model presented herein is fairly robust relative to r_1 variation, but much less robust relative to γ variation.

[0033] The results of the Table 2 are symmetric. There is no clinical reason to expect the same value for the mean absolute deviation, for example 184.0, for two different sets of parameters γ and r_1 i.e., (49.9, 4) versus (33.2, 36). However, this may be explained in the context of the model presented herein, by considering the general case and focusing on the estimation of the second residual r_2 . More specifically, the following two general cases may be considered: 1) over-specification of r_1 by δ and under-specification of γ by θ and 2) under-specification of r_1 by δ and over-specification of γ by θ . The estimation of r_2 for the two cases can be calculated from equation (9), with the actual r_2 provided as well.

$$\hat{r}_2 = a_{21}(r_1 + \delta) + a_{22}(\gamma - \theta) + a_{23}$$

$$\hat{\hat{r}}_2 = a_{21}(r_1 - \delta) + a_{22}(\gamma + \theta) + a_{23}$$

$$r_2 = a_{21}r_1 + a_{22}\gamma + a_{23}$$

[0034] In both cases, the absolute deviation is the same and equal to $|a_{21}\delta - a_{22}\theta|$. It follows that this symmetrical deviation applies to all r_i , $i \geq 2$. Furthermore, it is noted that if $a_{21}\delta - a_{22}\theta > 0$, the first scenario results in over prediction of r_1 , whereas the second scenario leads to under prediction of r_1 .

3. A Stochastic Extension

[0035] The exemplary illustrative prediction model presented herein may be extended to a stochastic, Bayesian framework, by considering probabilistic distributions for the key parameters r_1 and γ . For example, said parameters may follow the normal distribution, i.e., $r_1 \sim N(\mu_{r_1}, \sigma_{r_1}^2)$ and $\gamma \sim N(\mu_\gamma, \sigma_\gamma^2)$. The analysis is simplified since the parameters in the recursive equation (9) do not directly depend on either of these parameters. Since r_t is a linear combination of r_1 and γ it follows that r_t is also normally distributed, with the following distribution

$$r_t \sim N(a_{t1}\mu_{r_1} + a_{t2}\mu_\gamma, a_{t1}^2\sigma_{r_1}^2 + a_{t2}^2\sigma_\gamma^2).$$

[0036] Whereas in the previous analysis, a single value for r_1 and γ was specified with no resulting uncertainty to r_t , this exemplary model incorporates uncertainty into any given r_t , via the specified probabilistic distribution of r_1 and γ . The former deterministic approach may be considered as a special case of the latter stochastic approach with the variances of r_1 and γ set equal to 0.

[0037] The goal of adjusting observed electrolyte measurements collected via voiding is facilitated by using the quantiles of this distribution to obtain intervals for r_t . Towards this goal, two additional computations must be added to Algorithm 1.1 at step 3(d) and step 4(d). More specifically, in addition to the current calculation (which may be viewed as using the mean values of the prior distributions for r_1 and γ), the same computation is performed to calculate “upper-residuals” with initial values $(r_{1h}, \gamma_h) = (\mu_{r_1} + \sigma_{r_1}, \mu_\gamma + \sigma_\gamma)$ and “lower-residuals” with initial values $(r_{1l}, \gamma_l) = (\mu_{r_1} - \sigma_{r_1}, \mu_\gamma - \sigma_\gamma)$, where “h” refers to “high” and “l” refers to “low”. Thus, two additional sets of predicted residuals are determined to include uncertainty around the original predictions, thereby incorporating the real life uncertainty in specifying r_1 and γ , into the original predictions for the residual volumes.

[0038] It is noted that these uncertainty intervals are not constant over time, since the coefficients of the recursive equation (9) are time dependent. For example, considering the patient of Fig. 3, and specifying $r_1 \sim N(20, 5^2)$ and $\gamma \sim N(41.6, 1.2^2)$ instead of simply $r_1 = 20$ and $\gamma = 41.6$, the interval widths can be computed as (12, 27, 22, 37, 62) for the five timed measurements of Table 1 (following the first time point with the known value of r_1). The

center of these intervals corresponds to the true residual, since the input parameter distributions have been centered around the known value, i.e., 20 and 41.6.

[0039] Regarding the mean absolute deviation (“MAD”) of Fig. 4, the stochastic approach corresponds to creating an upper and lower confidence surface around the existing MAD surface. Furthermore, rather intuitively, when γ is under-specified, the upper residuals yield a lower MAD, and vice versa when γ is over-specified. Because of the robustness of the model relative to r_1 and γ , the specification of r_1 is dominated by that of γ for the values considered, thus even if γ is only slightly under-specified and r_1 is grossly over-specified, the upper residuals yield a lower MAD. Graphically, the surfaces corresponding to the upper and lower residuals reverse their ordering according to whether γ is over/under specified.

4. Estimation of r_1 and γ

[0040] Unknown residual volumes may be predicted using the RRE method presented herein. However, one must specify the values of r_1 and γ for each patient (or the mean and standard deviations of their distributions in the stochastic Bayesian framework) for implementing the method. The recursive equation may be used to determine feasible domains from which to choose these initial values that guarantee to produce realistic, i.e., positive values for the estimated residuals r_t . One approach would be to experiment with different starting values, but then this would have to be repeated for each patient. Instead, another approach followed in an exemplary embodiment is to consider the recursive equation $r_t = a_{t1} r_1 + a_{t2} \gamma + a_{t3}$ in conjunction with the constraint $r_t \geq 0$. Since the coefficients a_{ti} do not depend on either r_1 or γ , one can solve for said coefficients independently and graph each constraint $r_t \geq 0$ as a function of r_1 and γ . Each additional measurement interval incorporates an additional constraint, and consequently a feasible region. Intersection of all the feasible regions for all the measurement intervals yields feasible starting values for r_1 and γ , which guarantee positive residual volumes.

[0041] For example, Fig. 5 provides the restricted regions for the initial values of the simulated data for the five measured intervals for the simulated patient of Table 1. It can be seen from the above Figure that the true γ is very close to the region where the lines intersect, whereas the true r_1 is much less restricted. Similar patterns were noticed for other simulated patients. Hence, along with clinical information, these constraint diagrams may be used for parameter estimation with actual patients.

[0042] Although the feasible domain for the initial values may be large, it can be narrowed down to an one-dimensional search space, if the estimate for γ is taken with confidence. Based on the previous simulation results, the specification of γ may be more important with respect to the accurate estimation of the residual volumes. An approximate value of r_1 may be specified based on patient clinical data and important covariates such as age group.

[0043] In any given experiment, the mass collected at each time period may be calculated from the collected volume and concentration measurements. In one exemplary embodiment, γ may be estimated by averaging the collected creatinine masses collected each time period. Suppose the creatinine concentration in the residual volume from the previous period r_{t-1} is equal to the creatinine concentration in the new volume N_t . Furthermore, let γ_t^* be equal to the creatinine mass collected at t , and let $\gamma_t = \gamma$ equal the creatinine mass produced in the new volume, which remains constant every time period. Then $\gamma_t^* = \gamma$ when $r_{t-1} = 0$ and $r_t = 0$, i.e., there was no residual to begin with and everything was emptied. Furthermore, based on the initial assumption regarding concentration, $\gamma_t^* < \gamma$ when $C_t < N_t$, i.e., when the volume collected is less than the new volume produced. The condition $C_t < N_t$ is equivalent to an increase in the residual volume after voiding. Similarly, $\gamma_t^* > \gamma$ when $C_t > N_t$, i.e., when the volume collected is greater than the new volume produced, which is equivalent to a decrease in the residual volume.

[0044] γ may be also estimated in an iterative manner. Specifically, the predicted residuals can be used to adjust the collected measurements (as described above), and hence the creatine masses can be adjusted as well. The adjusted creatine masses are then averaged and serve as the estimate of γ , and the RRE method is run with this estimate of γ . In turn, new predicted residuals are produced, and these are used to similarly produce the next iterative estimate of γ , and so on. When the iterative estimate of γ has converged to a pre-specified limit, the iterative process is then stopped and calculates the predicted residuals corresponding to this γ estimate.

[0045] Although a patient may exhibit trends in residual behavior, the increase/decrease of the residual volume should be symmetrical. In other words, for any given point in time the probability that γ_t^* is less (or greater) than γ should be equal to 0.5, thus averaging the γ_t^* should produce an unbiased estimate of γ . This method (averaging) is unbiased if 1) the creatinine concentration in the residual volume from the previous period r_{t-1} equals the

concentration in new volume N_t ; or less strictly, the creatinine concentration in the new volume is not systematically higher/lower than that remaining from the previous time period, and 2) the residual volume is not systematically increasing or decreasing.

[0046] In an actual clinical trial, measurement error in either the creatinine concentration or the voided volume can lead to overestimating the residual volumes. As can be seen from equation (8), even a small measurement error can be carried forward in each iteration. Hence, the measurement of the creatinine and the voided volumes must be relatively accurate. However, it is noted that these measurements are easily performed and are quite accurate.

[0047] Furthermore, in an actual clinical trial, a patient may exhibit multiple voids during each time interval, e.g., each hour, instead of a single void at the end of the interval. In the exemplary embodiment presented herein, these multiple voids may be added together to produce the total volume voided for the interval. This does not affect the accuracy of the exemplary method. More specifically, assuming that the multiple void volumes mix properly, the lost information of the residuals during the multiple voids within the time interval are irrelevant. The only information needed is the last residual from the previous time interval, and the total volume collected, as well as the corresponding concentration.

[0048] Figure 6 illustrates an example computerized processing system for calculating an estimate of residual volumes of urine remaining in a patient's bladder in accordance with an exemplary embodiment. The system includes a computer processor 20 having at least inputs 21-24 for respectively receiving values for: an amount γ of a substance of secondary interest, such as creatinine, introduced per unit time into the patient's bladder, an initial residual volume r_1 (cc), voided concentration $Conc_{C_t}$ (mg/cc) of urine, and voided volume C_t (cc) of urine. Each of these inputs may be entered manually by a technician using keyboard 28 or other controller (e.g., mouse). Rather than being manually entered, the values for inputs 23 and 24 may be automatically provided by instrumentation which measures the voided volume and voided concentration, respectively. The values for r_1 and γ , input to the computer processor 20 at inputs 22 and 21, respectively, may be determined utilizing previous calculations by the computer processor 20 and/or utilizing the aid of another computer system.

[0049] The computer processor 20 utilizes inputs 21-24 to calculate coefficients of a recursive formula and to predict residual volumes of the patient's urine remaining in his/her bladder after voiding at predetermined times t in the manner described above (see, e.g., Figs. 2-

5 and associated written description above). The predicted residual volumes may be output by the computer processor **20** at output **25** and sent, for example, to a display monitor, printer for hard copy or another computer system for further processing. Also, the computer processor may utilize the predicted residual value(s) and the collected voided volume(s) C_t to estimate a volume of a substance of a primary interest, such as potassium, introduced in the patient's bladder as discussed above. See, e.g., formulas:

$$New\ Vol_t = C_t + r_t - r_{t-1};$$

$$New\ Vol\ Conc_t = \left(Conc_t - \frac{r_{t-1}}{C_t + r_t} Conc_{t-1} \right) \left(\frac{C_t + r_t}{New\ Vol_t} \right)$$

The value of the estimated volume of the substance of primary interest may then be output at output **26** to a video monitor, printer or another computer system for further processing.

[0050] The system illustrated in Fig. **6** also includes memory **30** for storing input and/or generated data. For example, all of the data input at inputs **21-24** or data generated for outputs **25-26** may be temporarily or permanently stored by memory **30**. Moreover, the memory **30** may store the calculated coefficients, recursive formulas, executable instructions and other data needed to perform the calculations described in accordance with the example embodiments of the technology described herein. All of the data stored in memory **30** may be sent to, accessed and/or utilized by the computer processor **20**.

[0051] The written description uses examples to disclose the exemplary embodiment, including the best mode, and also to enable any person skilled in the art to practice the exemplary embodiment, including making and using any devices or systems and performing any incorporated methods. The patentable scope of the invention is defined by the claims, and may include other examples that occur to those skilled in the art. Such other examples are intended to be within the scope of the claims if they have structural elements that do not differ from the literal language of the claims, or if they include equivalent structural elements with insubstantial differences from the literal language of the claims.

CLAIMS

What is claimed is:

1. A method for predicting one or more residual volumes r_t , for times $t \geq 2$, of urine remaining in the bladder after voiding at predetermined times t , comprising:

- a) specifying an initial value for a residual volume r_1 at time $t = 1$, and for an amount γ of a substance introduced per unit time into the bladder;
- b) measuring values of the collected voided volume C_t and its corresponding concentration $Conc_{C_t}$ of said substance after each voiding at times $t \geq 1$;
- c) calculating coefficients of a recursive formula based on measured values of b); and
- d) predicting the residual volume r_t , for times $t \geq 2$, after voiding according to calculations utilizing said recursive formula using said values of r_1 , γ , and the coefficients calculated in c).

2. The method according to claim 1, wherein the coefficients calculated in c) are:

$$\begin{aligned} \text{(a)} \quad a_{(t+1)1} &= a_{t1} \frac{Conc_{C_t}}{Conc_{C_{t+1}}} \\ \text{(b)} \quad a_{(t+1)2} &= a_{t2} \frac{Conc_{C_t}}{Conc_{C_{t+1}}} + \frac{1}{Conc_{C_{t+1}}} \\ \text{(c)} \quad a_{(t+1)3} &= a_{t3} \frac{Conc_{C_t}}{Conc_{C_{t+1}}} - C_{t+1} \end{aligned}$$

wherein $t \geq 1$.

3. The method according to claim 2, wherein the recursive formula in d) is:

$$\text{(d)} \quad r_{t+1} = a_{(t+1)1} r_1 + a_{(t+1)2} \gamma + a_{(t+1)3}$$

wherein $t \geq 1$.

4. The method according to claim 1, wherein the residual volumes r_t calculated in d) and the collected voided volumes C_t are used to estimate the volume of another substance, different from said substance, introduced in the bladder at time t according to the formula

$$New Vol_t = C_t + r_t - r_{t-1}, \quad t \geq 2.$$

5. The method according to claim 4, wherein the collected concentration of said another substance at time t is given by the formula

$$New\ Vol\ Conc_t = \left(Conc_t - \frac{r_{t-1}}{C_t + r_t} Conc_{t-1} \right) \left(\frac{C_t + r_t}{New\ Vol_t} \right)$$

and the amount of said another substance cleared from the bladder at time t is given by the formula

$$Mass_t = (New\ Vol_t) \times (New\ Vol\ Conc_t).$$

6. The method according to claim 1, wherein said substance comprises creatinine.

7. The method according to claim 4, wherein said another substance comprises potassium.

8. The method according to claim 3, wherein said parameters r_1 and γ comprise random variables having a normal probability distribution, such that

$$r_1 \sim N(\mu_{r_1}, \sigma_{r_1}^2) \text{ and } \gamma \sim N(\mu_{\gamma}, \sigma_{\gamma}^2).$$

9. The method according to claim 8, wherein the recursive formula is calculated for the following two sets of values:

$$(r_{1h}, \gamma_h) = (\mu_{r_1} + \sigma_{r_1}, \mu_{\gamma} + \sigma_{\gamma}) \text{ and } (r_{1l}, \gamma_l) = (\mu_{r_1} - \sigma_{r_1}, \mu_{\gamma} - \sigma_{\gamma})$$

thus providing stochastic intervals for the predicted values of r_t .

10. A system for predicting one or more residual volumes r_t , for times $t \geq 2$, of urine remaining in the bladder after voiding at predetermined times t , comprising:

a) a pre-determining unit for specifying an initial value for a residual volume r_1 at time $t = 1$, and for an amount γ of a substance introduced per unit time into the bladder;

b) an input for receiving measured values of the collected voided volume C_t and its corresponding concentration $Conc_{C_t}$ of said substance after each voiding at times $t \geq 1$;

c) calculating programmed logic circuitry for calculating coefficients of a recursive formula based on measured values of b); and

- 17 -

d) recursive calculating programmed logic circuitry for predicting the residual volume r_t , for times $t \geq 2$, after voiding according to calculations utilizing the recursive formula using said values of r_1 , γ , and the coefficients calculated in c).

11. The system according to claim 10, wherein the coefficients calculated by the calculating programmed logic circuitry are:

$$\begin{aligned} \text{(a)} \quad a_{(t+1)1} &= a_{t1} \frac{\text{Conc}_{C_t}}{\text{Conc}_{C_{t+1}}} \\ \text{(b)} \quad a_{(t+1)2} &= a_{t2} \frac{\text{Conc}_{C_t}}{\text{Conc}_{C_{t+1}}} + \frac{1}{\text{Conc}_{C_{t+1}}} \\ \text{(c)} \quad a_{(t+1)3} &= a_{t3} \frac{\text{Conc}_{C_t}}{\text{Conc}_{C_{t+1}}} - C_{t+1} \end{aligned}$$

wherein $t \geq 1$.

12. The system according to claim 11, wherein the recursive formula is:

$$r_{t+1} = a_{(t+1)1}r_1 + a_{(t+1)2}\gamma + a_{(t+1)3}$$

wherein $t \geq 1$.

13. The system according to claim 10, wherein the residual volumes r_t calculated by the recursive calculating programmed logic circuitry and the collected voided volumes C_t are used to estimate the volume of another substance, different from said substance, introduced in the bladder at time t according to the formula

$$\text{New Vol}_t = C_t + r_t - r_{t-1}, \quad t \geq 2.$$

14. The system according to claim 13, wherein the collected concentration of said another substance at time t is given by the formula

$$\text{New Vol Conc}_t = \left(\text{Conc}_t - \frac{r_{t-1}}{C_t + r_t} \text{Conc}_{t-1} \right) \left(\frac{C_t + r_t}{\text{New Vol}_t} \right)$$

and the amount of said another substance cleared from the bladder at time t is given by the formula

$$\text{Mass}_t = (\text{New Vol}_t) \times (\text{New Vol Conc}_t).$$

15. The system according to claim 10, wherein said substance comprises creatinine.

16. The system according to claim 13, wherein said another substance comprises potassium.

17. The system according to claim 12, wherein said parameters r_1 and γ comprise random variables having a normal probability distribution, such that

$$r_1 \sim N(\mu_{r_1}, \sigma_{r_1}^2) \text{ and } \gamma \sim N(\mu_\gamma, \sigma_\gamma^2).$$

18. The system according to claim 17, wherein the recursive formula is calculated for the following two sets of values:

$$(r_{1h}, \gamma_h) = (\mu_{r_1} + \sigma_{r_1}, \mu_\gamma + \sigma_\gamma) \text{ and } (r_{1l}, \gamma_l) = (\mu_{r_1} - \sigma_{r_1}, \mu_\gamma - \sigma_\gamma)$$

thus providing stochastic intervals for the predicted values of r_t .

19. The system according to claim 10, further comprising an automated measuring unit for measuring the collected voided volume C_t , and another automatic measuring unit for measuring the corresponding concentration $Conc_{C_t}$.

20. A method for predicting at least one residual volume of urine remaining in a patient's bladder after voiding, the method comprising:

specifying an initial value for a residual volume;

specifying an amount of a substance introduced per unit time into the bladder;

measuring a collected voided volume after a first voiding;

measuring a concentration of said substance in the voided volume after the first voiding;

measuring a collected voided volume after a second voiding, which occurred after said first voiding;

measuring a concentration of said substance in the voided volume after said second voiding;

- 19 -

calculating coefficients of a recursive formula based on the measured collected voided volume and the measured concentration of said substance after the first and second voiding, respectively; and

calculating a residual volume of urine remaining in the patient's bladder according to the recursive formula and the calculated coefficients.

21. The method according to claim 20, the method further comprising:

measuring a collected voided volume after a third voiding which occurs after the second voiding;

measuring a concentration of said substance in the voided volume after said third voiding;

re-calculating coefficients of the recursive formula based on at least the measured collected voided volume and the measured concentration of said substance after said second voiding and third voiding, respectively; and

calculating a second residual volume of urine remaining in the patient's bladder according to the recursive formula and the re-calculated coefficients.

22. The method according to claim 4, wherein said another substance comprises an electrolyte or a drug cleared by renal excretion.

23. The system according to claim 13, wherein said another substance comprises an electrolyte or a drug cleared by renal excretion.

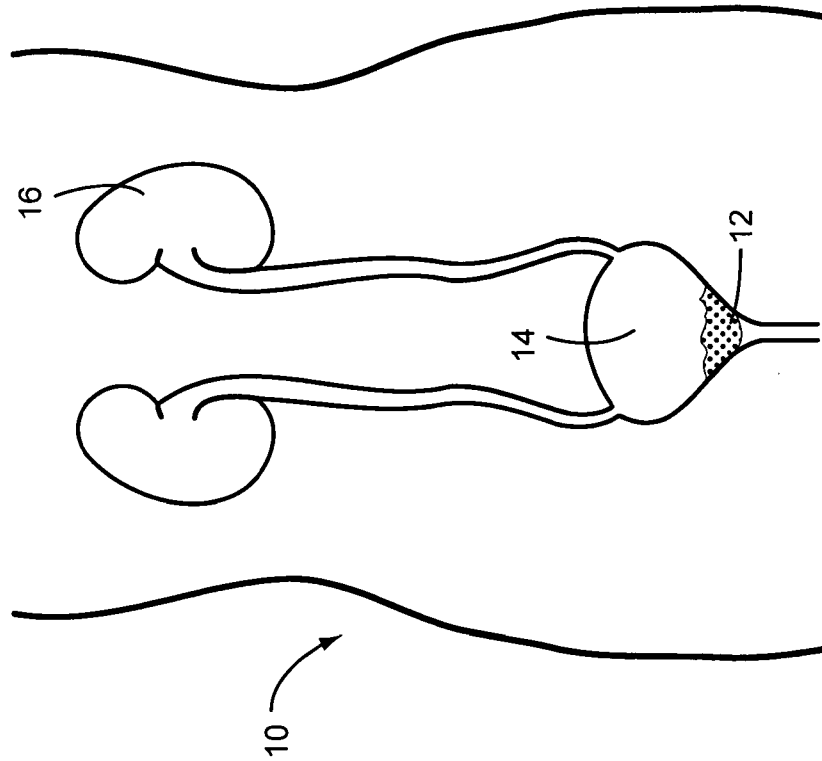


FIG. 1

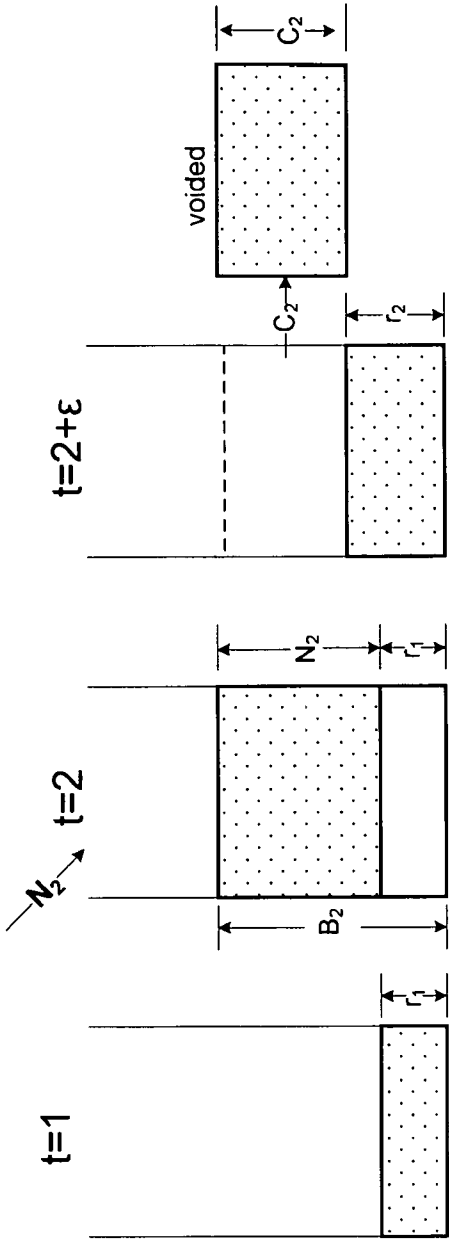


FIG. 2

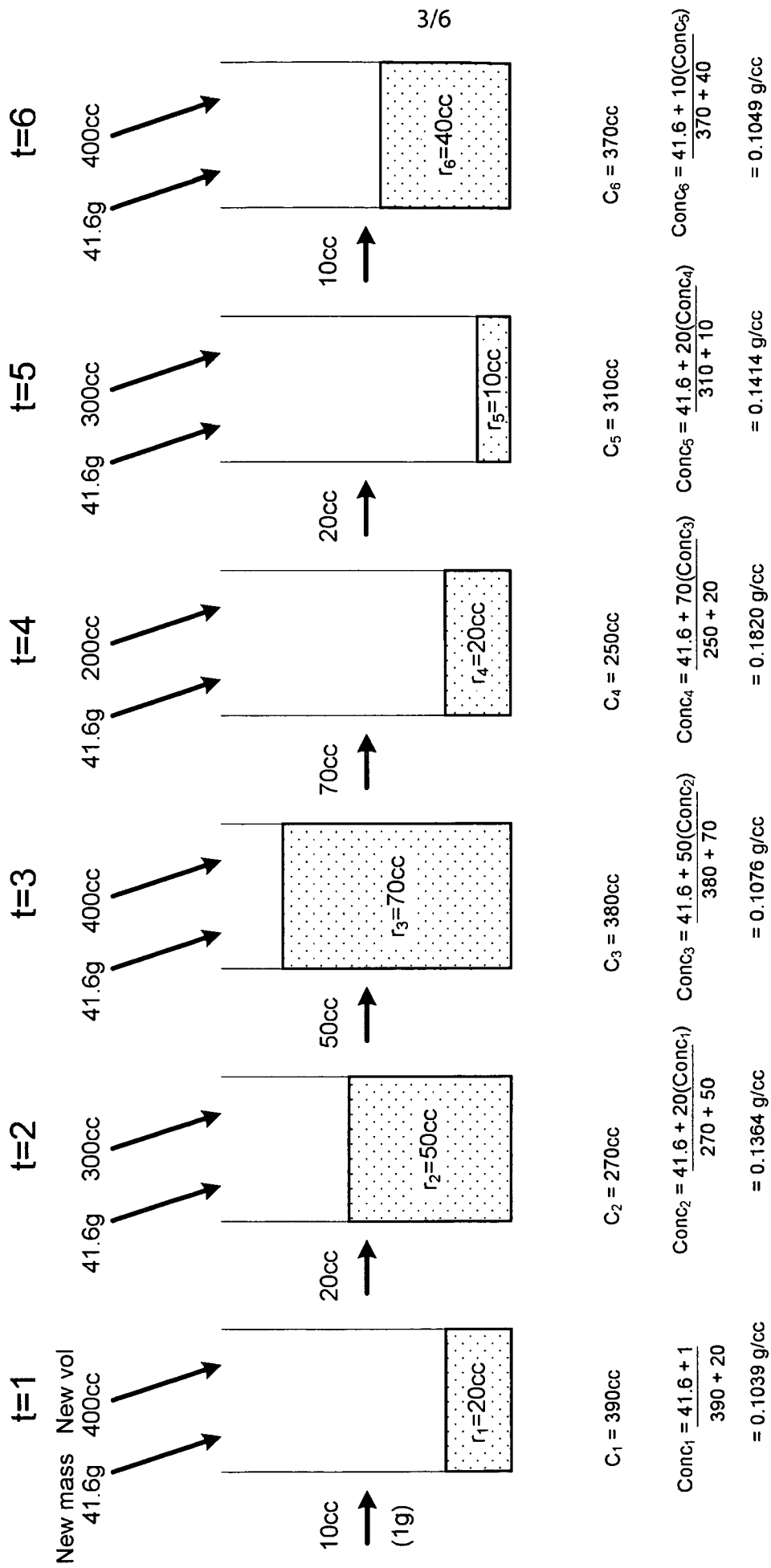


FIG. 3

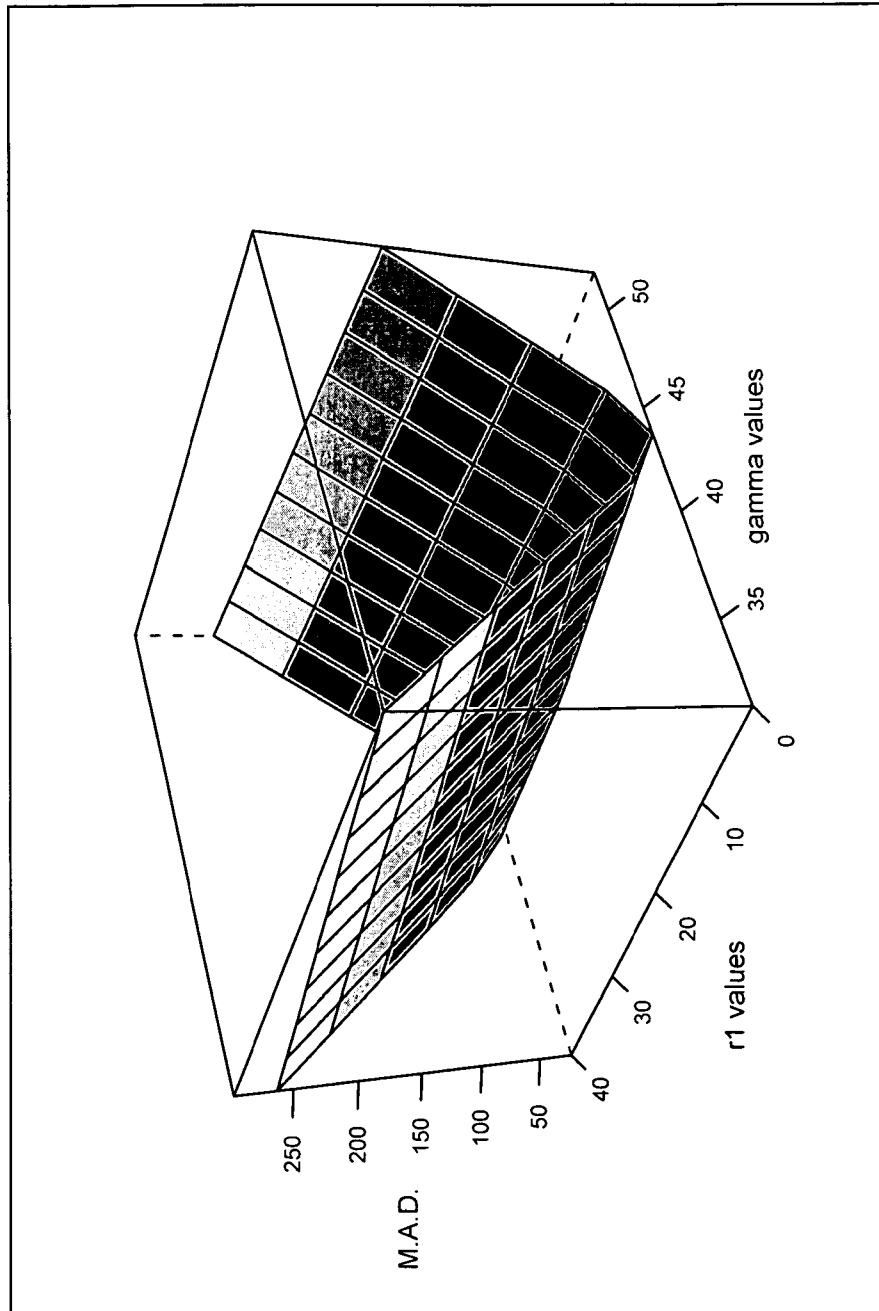


FIG. 4

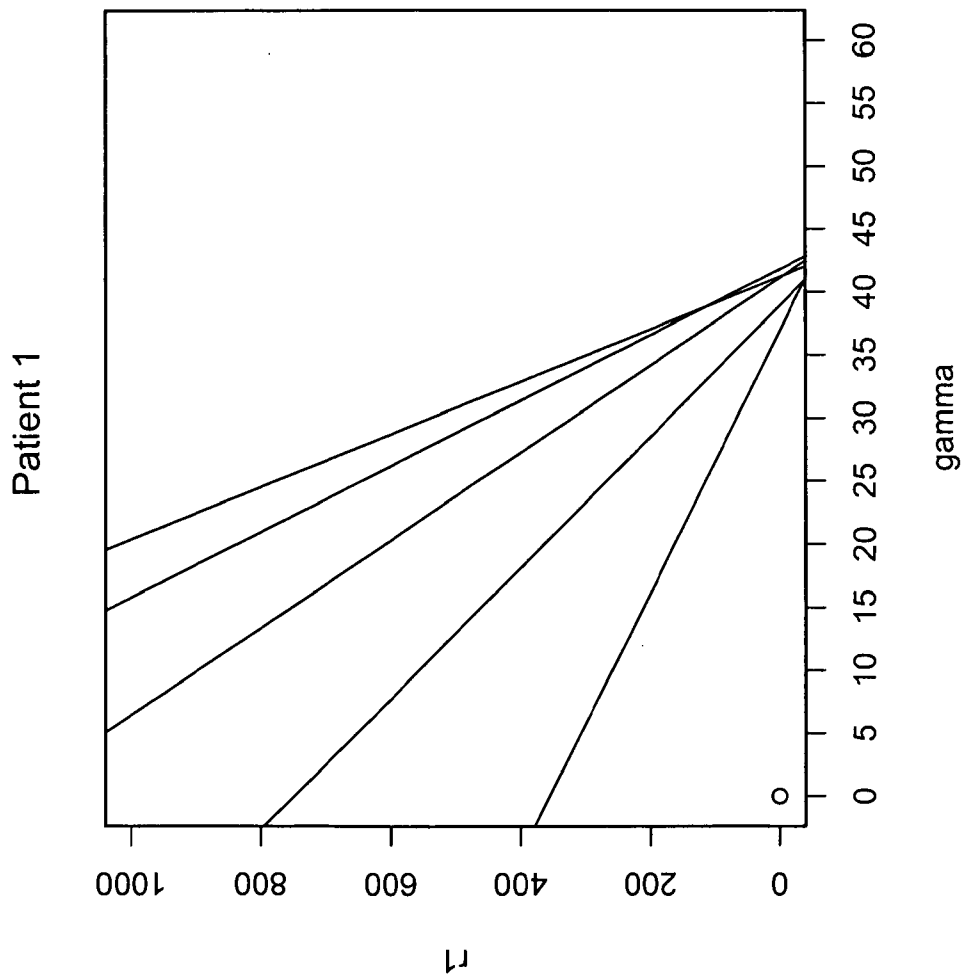


FIG. 5

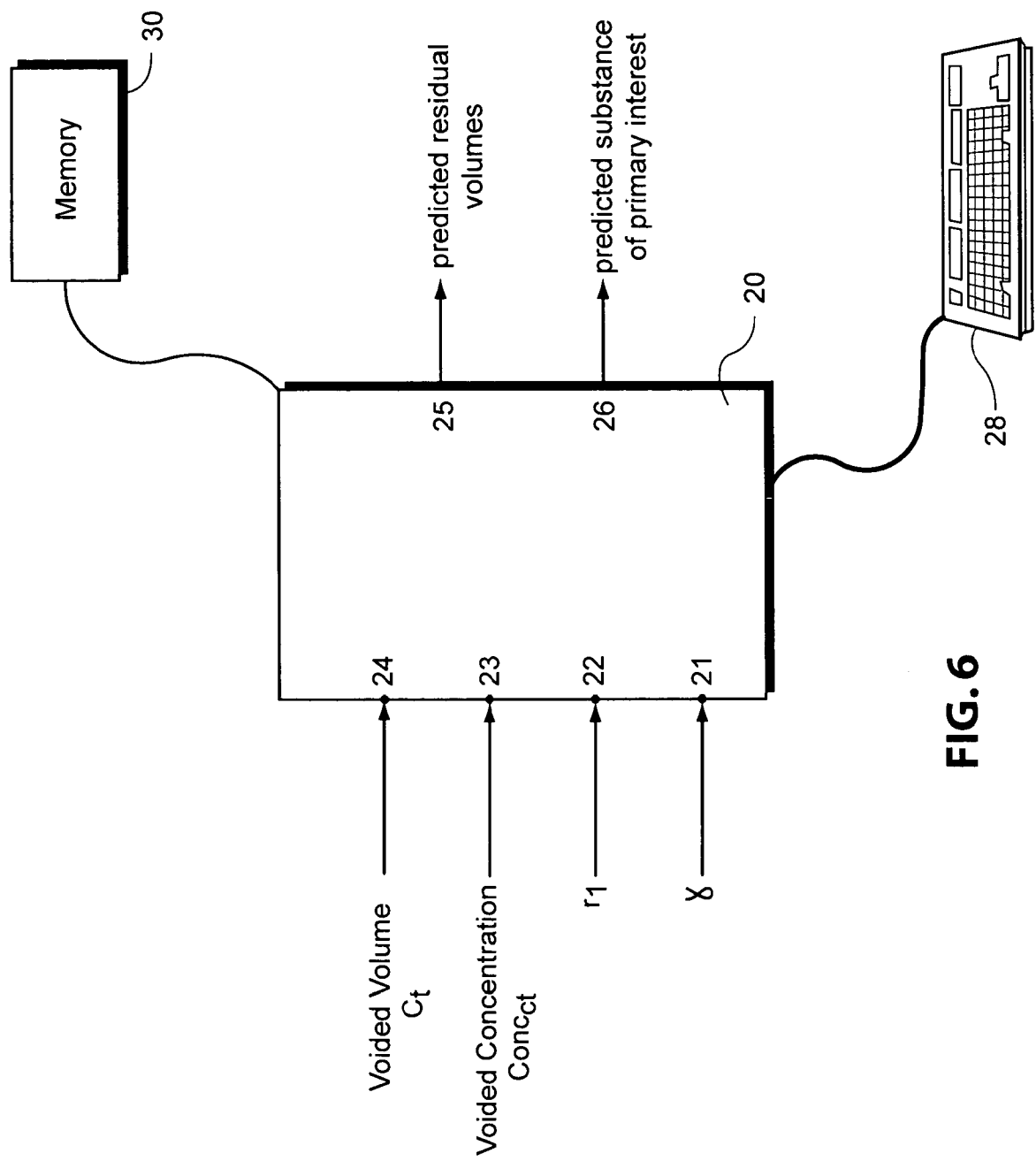


FIG. 6