Characterization of Intravenous Medication Administration in an Intensive Care Unit

by

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B.S., Electrical Engineering

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Submitted to the Department of Electrical Engineering and Computer Science in Partial Fulfillment of the Requirements for the Degree of Master of Science in Electrical Engineering

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Abstract

This project focuses on characterizing intravenous (IV) medication administration in an intensive care unit at a partner hospital. Information regarding IV medication dose was extracted from MIMIC II, a large database containing real patient data; this information was used to characterize the use of twelve hemodynamic drugs. Characterization was performed by extracting features such as maximum dose and overall shape from each trend plot. Additionally, because the administration of vasoactive drugs is generally accompanied by a change in blood pressure, several methods were explored of representing patient state by combining the mean blood pressure and drug dose trends to gain more information than can be obtained by each trend alone.

The results of drug use characterization show that an adequate picture of drug use can be gained by examining the characteristic shape of the dose trend in addition to features such as maximum dose administered. The patterns of medication administration have been shown to be indicative of overall patient state. The development of algorithms which match drug use trends to underlying physiology may aid in the annotation of large databases such as MIMIC II, and may also prove useful in tracking the hemodynamic state of a patient during his or her stay in intensive care.

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1 Introduction

In an intensive care unit (ICU) vast amounts of patient data are collected. Historically, this information has been used primarily by a patient's care team to track a patient's progress during his or her stay. Much of the data is also used by the hospital and insurance companies for billing purposes. Advances in monitoring equipment as well as data storage devices have made it possible to collect even more data and store it more efficiently.

The Harvard-MIT Laboratory for Computation Physiology is collecting, in real-time, patient data from acutely ill individuals in intensive care units at a partner hospital. The resulting database, named MIMIC II [1, 2], contains information such as nurses' notes, physiological waveforms (ECG, blood pressure), fluid balance, medications and laboratory test results from hundreds of patients. The diversity of stored data (waveforms, text, form data, etc.) provides a wealth of information, all of which is potentially useful to researchers for a variety of purposes.

Not only is it possible to collect and store huge amounts of real patient data, in the future it may be possible to synthesize this data in new ways to allow care staff to make better decisions regarding patient care, to detect deteriorating health earlier, or to make more accurate diagnoses. MIMIC II provides a powerful resource for developing and testing patient monitoring algorithms which could aid caregivers in incorporating the large amount of information available into diagnosis and treatment. For example, one of the most difficult tasks for humans to perform is to pull out patterns in multiple sets of trend data and compare them to each other. In the ICU, this is exactly the kind of task that is performed when monitoring blood pressure response to a change in medication dose or when comparing diastolic pulmonary artery pressure and cardiac output to assess changes in cardiac contractility.

1.1 MIMIC II

MIMIC II is a large-scale database consisting of real patient data collected from individuals in intensive care units. The database consists of two parts. Form data and free text such as lab results, medications administered, and nurses' notes are stored in a postgreSQL relational database. Nursing stations in the ICU are equipped with a Philip's CareVue terminal where caregivers enter this type of information. The CareVue data is stored on the hospital side in an Information Support Mart built around Oracle technology. It is then downloaded directly from the Oracle database, deidentified, and entered into MIMIC II. Waveforms such as ECG and blood pressure are recorded by patient monitors that are not connected to the CareVue nursing stations. This data is downloaded from a waveform collection system at the hospital and stored separately from the CareVue data.

1.2 Database-supported Monitoring Algorithm Development

One focus at the Laboratory for Computational Physiology is the development of advanced patient monitoring algorithms for tracking the evolution of a patient's hemodynamic state throughout the course of his or her stay. Using new data processing algorithms, these monitors would integrate many different types of available data such as waveforms, physiologic parameters, nursing notes, and laboratory values. Based on continuous analysis of this data, the care team would be presented with a constant assessment of patient state, predictions regarding the trajectory of that state, alarms to indicate when the trajectory has exceeded certain

boundaries, and diagnostic hypotheses to explain the cause of abnormal findings. MIMIC II will provide the data needed to develop and train these applications.

1.3 Database-supported Algorithm Testing

Testing of advanced patient monitoring algorithms requires performance evaluation against a "gold standard." For example, before it is possible to determine whether a new algorithm provides fewer false alarms, it is necessary to provide a data set in which all alarm occurrences are labeled as either true or false. In general, labeling for this type of evaluation requires human experts to annotate key events in real patient data. MIMIC II has the potential to provide such data for a variety of different event-detection algorithms. To aid in evaluation of an advanced patient monitor such as the one described in the previous section, the lab plans to provide many different types of annotations in MIMIC II. These include identifying true and false alarms, assessing hemodynamic state and trajectory for each patient, and coding the clinical rationale behind diagnostic or therapeutic interventions. The large size of MIMIC II makes annotating the entire database a non-trivial task.

1.3.1 Database Annotation

To further the process of annotation, several methods have been proposed. All hinge on recognizing clinically significant events given the raw information contained in the database. One method is to locate where diagnostic or therapeutic interventions were performed, another is to look for significant patterns in the trends of physiological waveforms, and a third involves searching the nurses' notes for important information. Eventually, all three methods, and possibly others, can be combined for faster and more accurate annotating.

Because waveform trends are highly variable between patients, the false alarm rate is likely to be high for any detection algorithm which relies solely on locating patterns in these trends. Likewise, processing of the free text contained in the nurses' notes is a very complex and difficult problem. Locating where interventions occur is thought to provide one practical method of automatically detecting clinically significant events. An intervention is an event such as an intubation, an insertion of a Swan-Ganz catheter, a change in ventilator settings, a change in medication dose, or a change in the rate of IV fluid administration. When the care team recognizes a change in the condition of the patient, a diagnostic or therapeutic intervention is usually performed. These events will all be documented in the database in some form.

1.4 Problem Statement

This project focuses on intravenous (IV) medications. In the ICU, many of the most potent drugs are administered intravenously. The administration of these drugs should be followed by a detectible change in patient state – i.e. changes in blood pressure, ECG waveforms, fluid balance, etc. Interventions such as IV drug changes also signal points at which the care team felt that new therapies were required to improve patient state. Therefore, interventions should be preceded by detectible changes in patient state. The changes in patient state both preceding and following IV medication administration have clinical significance as well as significance in training patient monitoring algorithms and should therefore be accompanied by an annotation in the database.

This project can be broken into three tasks. First, to aid in database annotation, information regarding IV medication dose was extracted from MIMIC II and plotted. Once this information was available, the use of each drug over the patient population was characterized based on features extracted from the drug dose trend plots. Finally, because the administration of vasoactive drugs is generally accompanied by a change in blood pressure, several methods were explored in which mean blood pressure and drug dose information were combined to gain insight into the evolution of patient response over time. Each of these tasks is discussed in more detail in the following sections.

1.4.1 Locating Intravenous Medication Changes

One of the primary goals of this project is simply to locate when intravenous medication changes occurred during a patient stay. Locating these changes is expected to aid database annotation by identifying points at which the care team felt a change in patient state warranted an intervention. Labeling these patient state changes is critical for development and testing of successful detection algorithms. The focus of research at the Laboratory for Computational Physiology at MIT is primarily on cardiovascular system modeling, monitoring and assessment. Therefore, this project focuses on a subset of IV medications which affect hemodynamics. These drugs and a brief description of their uses are listed in Table 1. Chapter 2 gives more detail regarding extracting and plotting dose information from MIMIC II.

Table 1. Hemodynamic Medications Examined

Medication	Use
Amiodarone [3,4,6]	An antiarrhythmic drug given to treat and prevent ventricular fibrillation and tachycardia and often atrial fibrillation.
Dopamine [5]	A β-receptor agonist which in low doses stimulates blood flow and modestly increases cardiac contractility; in high doses the primary effect is vasoconstriction. Used in the ICU to treat hypotension due to shock or shock-like states.
Dobutamine [5]	A β1-receptor agonist which increases cardiac contractility and causes mild vasodilation, used to treat cases of systolic heart failure.
Heparin [7]	An anticoagulant used to treat and prevent occurrence of blood clots.
Lasix [3, 8]	A potent diuretic used to reduce fluid overload in cases such as congestive heart failure or renal disease.
Levophed [5]	An α-receptor agonist which causes widespread vasoconstriction, added as a second drug after Dopamine in cases of septic shock.
Milrinone [3, 4]	A positive inotropic agent which stimulates the heart and relaxes vascular smooth muscle (causing vasodilation), used to treat congestive heart failure.
Neosynephrine [3,9]	A vasoconstrictor and pressor with effects similar to Levophed, used to treat cardiac shock states.
Nitroglycerine [5]	Relaxes vascular smooth muscle causing vasodilation, used to treat hypertension combined with low cardiac output.
Nitroprusside [5]	Similar effects as nitroglycerine, used to treat severe hypertension combined with low cardiac output.
Propofol [10]	An anesthetic used in the ICU to sedate patients on ventilation.
Vasopressin [11,12]	An antidiuretic hormone which also causes vasoconstriction, use in the ICU may indicate septic or hemorrhagic shock.

1.4.2 Characterizing Hemodynamic Medication Use in the ICU

Once the dose information is available for each patient, it is possible to characterize the use of medications of interest. Besides providing an interesting summary of drug usage patterns at the partner hospital, it may be possible to use these patterns as indicators of overall patient state or underlying pathology. Because neither patient state nor underlying pathology is explicitly included in the database, patient mortality in the ICU was used as an imprecise indicator of overall patient state. To correlate usage patterns to outcome, patient populations were distinguished based on the administration of one of the twelve hemodynamic drugs of interest (see Table 1) and several features were compared between patients who died in the unit versus those who were transferred, sent home, sent to rehabilitation facilities, or otherwise discharged alive. This process is described in Chapter 3.

1.4.3 Viewing History of Patient Response to a Medication

MIMIC II is a powerful resource because it allows multiple parameters to be combined to extract information that would be difficult or impossible to keep track of using traditional data entry methods. As mentioned, one long-term goal of the lab is to synthesize much of the available patient data to present a coherent representation of overall patient state and its development over time. For example, one of the primary responses to vasoactive medications is a change in mean blood pressure. Traditionally, medication dose and blood pressure measurements are recorded, and the caregiver will have a good idea of how a patient has been responding to a drug within the last few hours. However, identifying patterns in these two trends which occur over a longer time scale, and relating the patterns to each other, is practically impossible for a busy doctor or nurse to do rapidly and effectively. In this project, blood pressure response is combined with drug dose information to present a more complete picture of patient state than could be obtained from each trend alone. Three ways of presenting blood pressure and drug dose information are explored which could allow the care team to make use of an evolving trend rather than just current conditions.

2 Locating IV Medication Changes in MIMIC II

MIMIC II is a postgreSQL relational database containing real patient data collected from individuals in the intensive care units of a partner hospital. As of January 2004, the database contains nurses' notes, lab results, medications, waveform trends, and more for over 1700 patient-stays. With the exception of the waveforms and numeric trends (ECG, blood pressure, etc.), this data is stored in tables within the postgreSQL database. Information from these tables can be used to derive IV medication dose as a function of time, and this process is detailed in Section 2.1. Several other tables deal with intravenous medication administration, and these are examined in more detail in Appendix A.

2.1 Plotting IV Medication Dose versus Time

The relevant fields in the `medevents` table include `pid`, `itemid`, `charttime`, `dose`, and `doseuom`, as seen in Figure 1a. This table contains many more fields which were not required for this project, and these are described in more detail in Appendix A. The `pid` is the unique number assigned to each patient upon admission to the ICU. This number is used to link information pertaining to a particular patient-stay once identifying information such as the

patient's name has been removed from the record. The `itemid` uniquely identifies the medication given to the patient; the `d_meditems` table links the `itemid`s to their labels (see Figure 1b). For example, an `itemid` of 128 corresponds to the drug Neosynephrine. It is also evident from Figure 1 that the `medevents` table contains information on many medications other than the twelve examined in this project. The `dose` and `charttime` columns indicate the intravenous medication dose that was being administered and the time at which the dose was recorded. The `doseuom` identifies the units of measure which correspond to the recorded medication dose.

a.

pid	itemid	charttime	dose	doseuom
37.000000	115.000000	2001-03-27 20:45:00-05	10.000000	mghr
37.000000	115.000000	2001-03-27 21:00:00-05	10.000000	mghr
37.000000	115.000000	2001-03-27 21:30:00-05	10.000000	mghr
37.000000	128.000000	2001-03-16 16:00:00-05	1.000000	mcgkgmin
37.000000	128.000000	2001-03-16 16:15:00-05	1.000000	mcgkgmin
37.000000	128.000000	2001-03-16 17:00:00-05	1.000000	mcgkgmin

b.

itemid	label
115.000000	Diltiazem
128.000000	Neosynephrine-k

Figure 1. *Sample data from* ***a.*** *the* `medevents` *table in MIMIC II and* ***b****. the* `d_meditems` *table in MIMIC II, which matches* `itemid`*s in* `medevents` *to their corresponding labels.*

Dose and time information for each drug given to each patient was extracted from the `medevents` table and stored in a multidimensional array in MATLAB, which was used to do all the data processing and plotting. Figure 2 shows the relationship between the `charttime` and `dose` information recorded in `medevents` and the time course of the dose during the course of the patient's stay. The stem plot shows the doses recorded in `medevents`; these are sampled and held using MATLAB's `stair()` function to obtain the continuous plot of dose over time. Note that the samples are taken at irregular intervals and up to two hours apart.

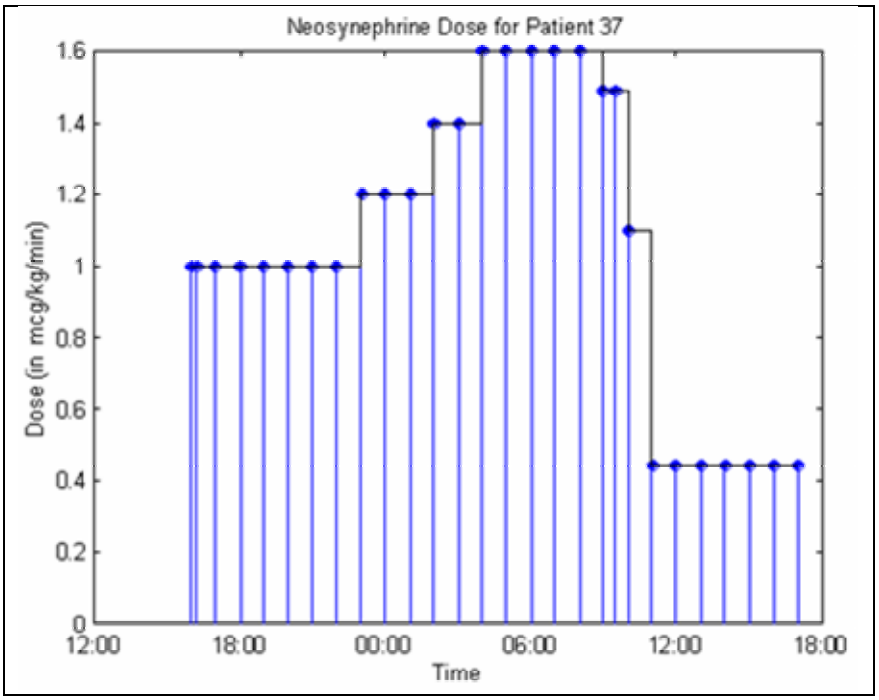


Figure 2. *Medication dose versus time information for one of the patients in MIMIC II. Stems and open circles represent samples taken directly from the* `medevents` *table. Solid black line represents continuous plot of dose over time, obtained by sample and hold. Note that dose recordings are not evenly sampled.*

3 Characterizing Drug Use in the ICU

To characterize the use of hemodynamic medications, features were extracted from each of the time course plots. For each patient given one of the twelve drugs analyzed, the maximum dose, average dose, and total length of time of administration were found. Extraction of these features is described in Section 3.1.1. In addition, each plot was assigned a number which corresponded to an overall shape; this characterization is described in Section 3.1.2.

Feature extraction not only allows characterization of drug usage among the total population of patients who received a particular drug, but it also provides a way to compare drug use between subpopulations of patients. For some drugs, usage patterns differ depending on the underlying disease being treated, and thus can be a good indicator of overall patient state. For the purposes of this project, because underlying pathology is unknown, patient outcome is used as an indicator of patient state. It is expected that for some drugs, the doses administered or the total length of time of administration may be higher among patients who died in the ICU, who are assumed to be in poorer health than those who left the unit alive.

To determine the discharge status of a particular patient, the `disch_status` table in MIMIC II was used. This table is sparsely populated and some of the entries are rather ambiguous. Patients who had a discharge status of "transfer," "home," or whose field was left blank were assumed to have left the unit alive, and a sample of these cases was confirmed by inspecting the last available nursing note for these patients. Patients with a discharge status of "other" were inspected by hand, and these were generally found to correspond to patients who were transferred out of the unit. Patients who died in the unit had a discharge status of "deceased" or "no discharge status" entered in the table, and each of these cases was confirmed by inspection of the last available nursing note. In about half of the cases when "no discharge status" was entered into the table, the last available note gave no indication of improving health, the

possibility of transfer, or the time of death. Because these cases could not be confirmed to have come from surviving or deceased patients, they were excluded from the populations characterized. Forty-three patients, or approximately 7% of the patients administered one of the twelve drugs of interest, fell into this category.

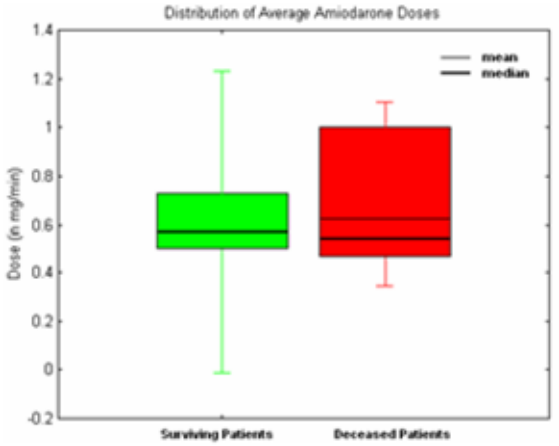
3.1 Characterization Methods

To correlate usage patterns to outcome, patient populations were distinguished based on the administration of one of the twelve hemodynamic drugs of interest. Several features were extracted from each dose trend, and the overall shape of the trend was characterized. These methods are described in more detail in Sections 3.1.1 and 3.1.2, respectively. Patterns of drug use were compared between patients who died in the unit versus those who were transferred, sent home, sent to rehabilitation facilities, or otherwise discharged alive.

3.1.1 Feature Extraction

Maximum dose, average dose, and total time administered were obtained for each patient given one of the twelve drugs listed in Table 1. The values of these features across the populations of deceased and surviving patients were represented by creating boxplots (see Figure 3). The boxes cover the middle 50% of data values, while the whiskers indicate low and high extremes. The population mean is denoted by a thin black line spanning the box, while median is denoted by a thick black line. Two-sample two-tailed *t* tests were performed to compare the values of each feature in surviving populations to those in the deceased populations.

Figure 3. *Sample boxplot characterizing drug use among surviving patients and deceased patients.*



3.1.2 Shape Characterization

In the ICU, a patient whose condition is improving will generally be weaned off of a vasoactive drug while a patient whose condition is worsening may be given increasing doses toward the end of life. For this reason, it was important to capture the overall shape of the dose trend in addition to the features listed in 3.1.1. Because the timescale of patient response can be highly variable, as is the weaning or dosage increase process toward the end of drug administration, the entire record was classified into an abstracted shape, regardless of length. Each plot was fit to an overall shape consisting of at most two line segments. The possible shapes are shown in Figure 4. Some shapes were hypothesized to indicate a worse patient state than others. Generally, a monotonically decreasing shape is thought to be better than one which starts and ends in the same place, which is in turn thought to be better than one which only increases.

Each of the time course plots was fit to one of these abstracted shapes according to the following algorithm. First, a line was drawn between the first non-zero dose and the last non-zero dose in the record. The last non-zero dose was used because it was necessary to capture more specific information about the pattern of use toward the end of the record. When a drug is weaned off due to improved patient state, the last recorded dose is usually 0. However, in cases of severe decline in patient health, when the care team decides that heroic efforts are no longer warranted, IV medication doses will also be set to 0 before the patient's death. Simply using the last recorded dose would make it impossible to differentiate between these two physiologically different cases. A breakpoint was defined in the record as the time at which the recorded dose differed from this line by the greatest amount. The two line segments comprising the abstracted shape then went from the starting dose to the breakpoint and from the breakpoint to the last non-zero dose. Figure 5a-b illustrates this process. The first dose change, second dose change, and location of the breakpoint as a percent of the total length of the record were stored to characterize the overall shape. The starting dose and length of record were also stored to allow construction of a more accurate approximation to the actual record.

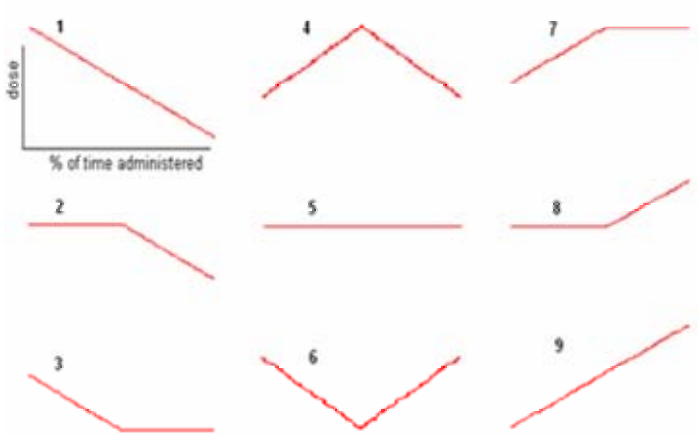


Figure 4. *Nine possible two-segment shapes. Each time course plot was fitted into one of the 9 categories.*

To further ensure grouping of physiologically-like records, several refinements were made to the above method. Line segments corresponding to very small dose changes were approximated with flat lines. "Very small" was defined as less than 5% of the average dose given. Physiologically, a rapid increase in dose at the beginning of a record followed by a continuous decline in dose indicates a good response by the patient, and has more in common with category 1 than category 4. Similarly, a rapid decrease in drug dose followed by a continuous increase is more like category 9 than category 6. To capture this, if the breakpoint occurred in the first 5% of the record, the record was categorized by the second dose change only. Practically speaking, this means that shapes which might have fallen into categories 6 or 4 were recategorized into 1 or 9 respectively. Performing a similar operation if the breakpoint is close to the end of the record is difficult, as the end of the record is most likely to correlate with patient outcome. These cases were not recategorized.

This method works well except in cases where the drug is shut off for a period of time before being turned back on. Generally, this occurs in very long records, where a drug must be shut off for safe use, or when the patient stabilizes for several hours or days, but then begins to require medication again. To characterize cases where a drug was shut off for more than 30 minutes, only the time after the drug was resumed was considered. It is assumed that events that happen later in the record will more accurately correlate with patient outcome, while those which happen very early in the record are less indicative of the physiological state at the time of discharge.

Figure 5c shows an example in which only the latter part of the record has been considered in obtaining the abstracted shape. Regions of drug discontinuation which were shorter than 30 minutes in duration were ignored in characterizing the overall shape; an example is shown in Figure 5d.

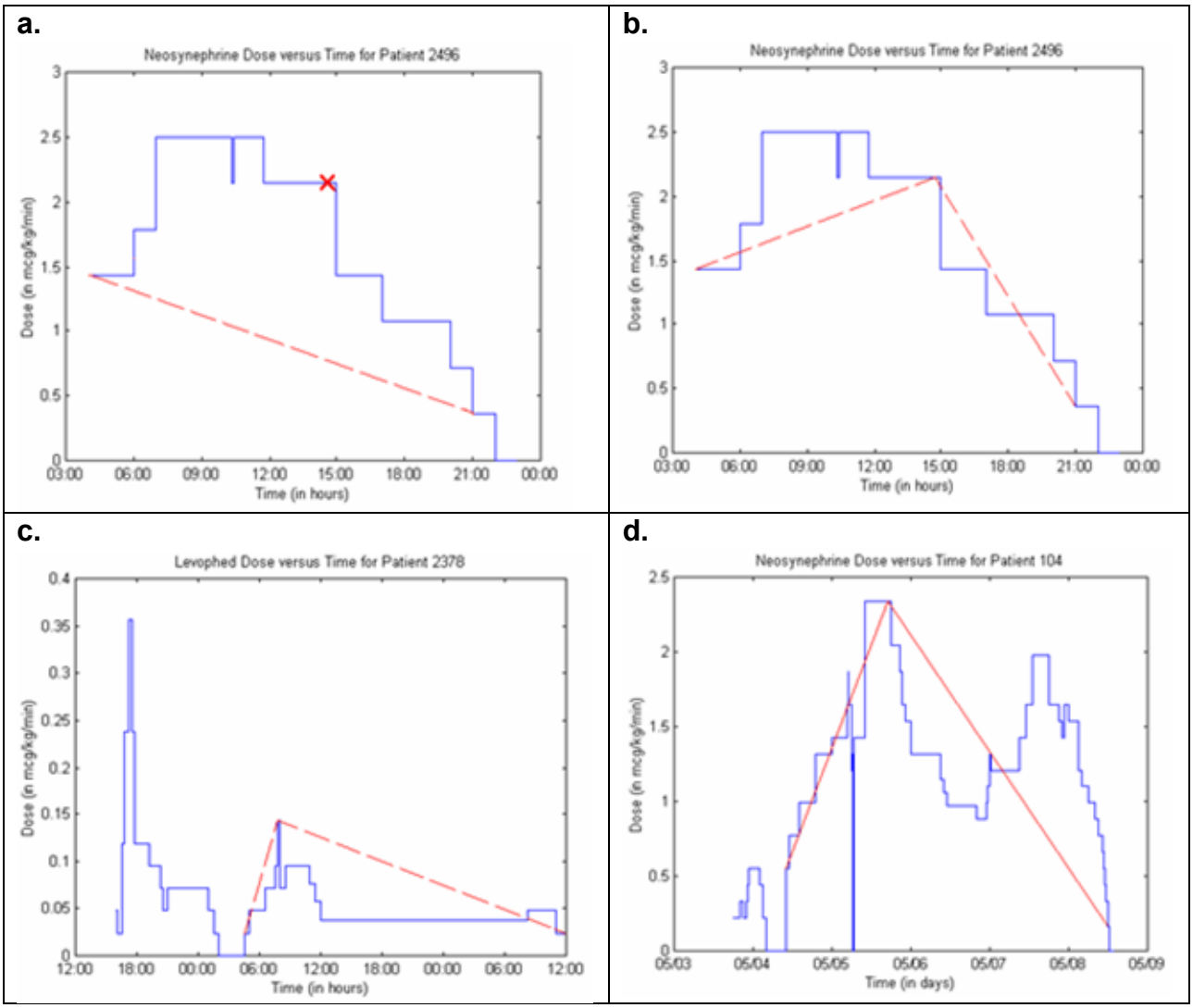


Figure 5. *Abstraction of overall shape from dose time course plot.* ***a.*** *Breakpoint (denoted by red x) is found by taking recorded trend value which is farthest from line connecting first and last recorded non-zero doses (dashed line).* ***b.*** *Overall shape characterized by two lines (dashed lines). Three numbers completely characterize time course: first dose change, breakpoint location and second dose change.* ***c.*** *Case where original method is insufficient for characterization. In this case, only the final part of the record is considered.* ***d.*** *Case where drug is resumed less than 30 minutes after being stopped. This part is ignored in characterizing the overall shape.*

3.2 Characterization Results

All characterizations were performed on a version of MIMIC II which contains 955 patients. Of these, approximately 2/3 received at least one of the hemodynamic drugs of interest (606/955). Figure 6a shows the percent of patients receiving each of the twelve drugs examined, while

Figure 6b shows the probability of survival for patients on each drug, compared to the overall probability of survival for the entire database.

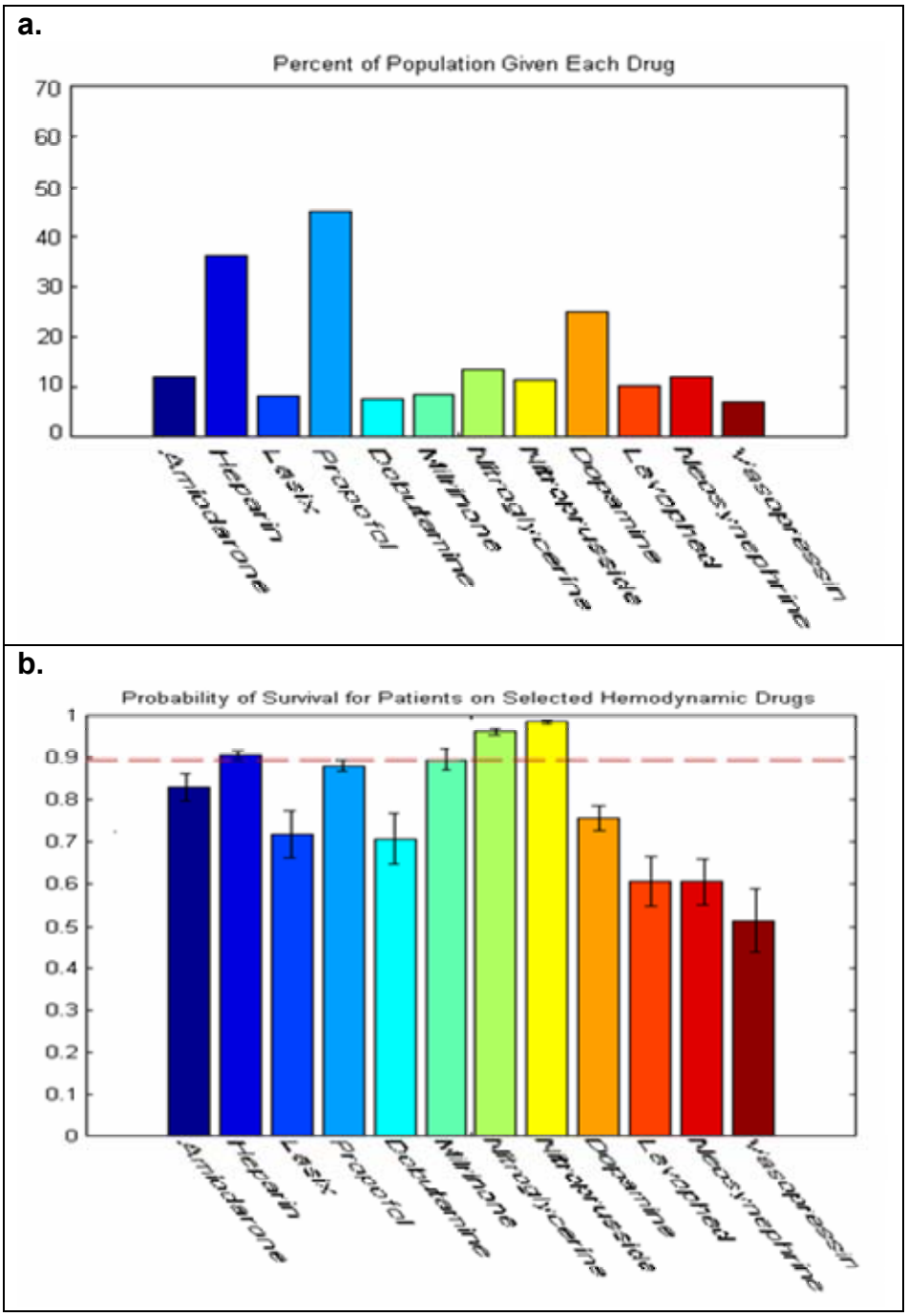


Figure 6. ***a.*** *Percent of patients in the total population given selected hemodynamic medications* ***b.*** *Percent of surviving patients for each medication. Dashed red line represents percent of surviving patients in total population. Total number of patients receiving at least one of the 12 hemodynamic medications equals 606.*

From Figure 6b, we see that the probabilities of survival associated with Heparin and Propofol are very similar to the entire database, as would be expected for these two drugs. Intravenous Heparin is generally used for prevention of blood clots in a large portion of the ICU population

(Figure 6a); it is reasonable that the use of such a preventative medication would not indicate patient conditions for which the probability of survival differed substantially from the entire population. Propofol is used to sedate patients who are placed on ventilators. Because placement on a ventilator does not necessarily indicate a particular critical pathology, it is not surprising that the probability of survival for Propofol matches that of the entire population. The probability of survival for the vasodilators, Nitroglycerine and Nitroprusside, were found to be higher than that of the entire ICU population. One could speculate that this is due to one of two possibilities: 1) cases of hypertension where these drugs are used are not immediately life-threatening, or 2) the use of nitrovasodilators is extremely effective at reducing and stabilizing patient blood pressure. In contrast to the high probabilities of survival associated with vasodilator use, all four vasoconstrictors (Dopamine, Levophed, Neosynephrine, and Vasopressin) are associated with lower-than-average probabilities of survival. This could be due to the fact that severe hypotension due to shock or hemorrhage, for which these drugs are administered, is associated with the most critical patient conditions. The underlying pathology in these cases is often not changeable with the administration of drugs which primarily affect peripheral resistance.

3.2.1 Non-vasoactive Drug Use Characterization

Four non-vasoactive drugs were characterized: Amiodarone, Heparin, Lasix, and Propofol. With vasoactive drugs, one would expect the doses to be carefully regulated in response to changes in a patient's blood pressure. Because the dose is closely related to the patient's hemodynamic state in this way, one might expect populations of deceased patients to have different usage patterns than those of survivors. Some of the non-vasoactive drugs, including Amiodarone, Heparin, and Propofol, are not as closely tied to acute changes in patient state, thus it is expected that usage patterns may be similar between deceased and surviving patients. IV Lasix is used in cases of severe congestive heart failure and usage patterns for this drug are likely to differ between deceased and surviving patients.

3.2.1.1 Amiodarone

Amiodarone [3, 4, 6] is an anti-arrhythmic drug given to patients to stabilize and prevent abnormal ventricular rhythms, and is often used in cases of atrial fibrillation. Its primary action is to slow electrical conduction in the atrioventricular node, and it is administered either intravenously or orally. In the case of intravenous administration, medical literature indicates that a high loading dose of around 5 mg/kg is given to the patient initially, followed by a low maintenance dose of about 5 μg/kg/min. Patients generally respond to the drug in 48-96 hours, but Amiodarone can safely be given for longer periods. Oral Amiodarone is often administered chronically after intravenous use ends. Because the use of Amiodarone is not associated with life-threatening problems, it is not expected that usage patterns should differ between populations of surviving and deceased patients.

Sixty-five cases in MIMIC II received intravenous Amiodarone; this corresponds to approximately 7% of the ICU population (65/955). Eleven of these patients died in the unit. Figure 6a-c shows the typical usage patterns for Amiodarone patients. The average dose is around 6 μg/kg/min and the typical length of intravenous administration is under 100 hours, though the drug was administered for over 10 days in some cases; these numbers are similar to those found in the literature. Two-sample, two-tailed *t* tests confirm that maximum and average

drug doses as well as administration time are not significantly different between the two populations (α=0.05, P_{max}=0.34, P_{ave}=0.80, P_{time}=0.40). Figure 7d shows the classification of the characteristic shape of drug dose administration in the populations of survivors and deceased patients. For plotting convenience, shapes 1, 2, and 3 (see Figure 4) have been combined into one "generally decreasing" category and shapes 7, 8, and 9 have been combined into a "generally increasing" category. We see that the general usage patterns are similar between populations of survivors and non-survivors, as expected. It should be noted that with 11 deceased patients, the estimates concerning the percent of the population in any particular category is subject to high variance. Figure 7e shows the probability of survival associated with each shape category. Due to the high variance in some categories, these probabilities cannot be said to differ significantly from the overall probability of survival for patients receiving Amiodarone.

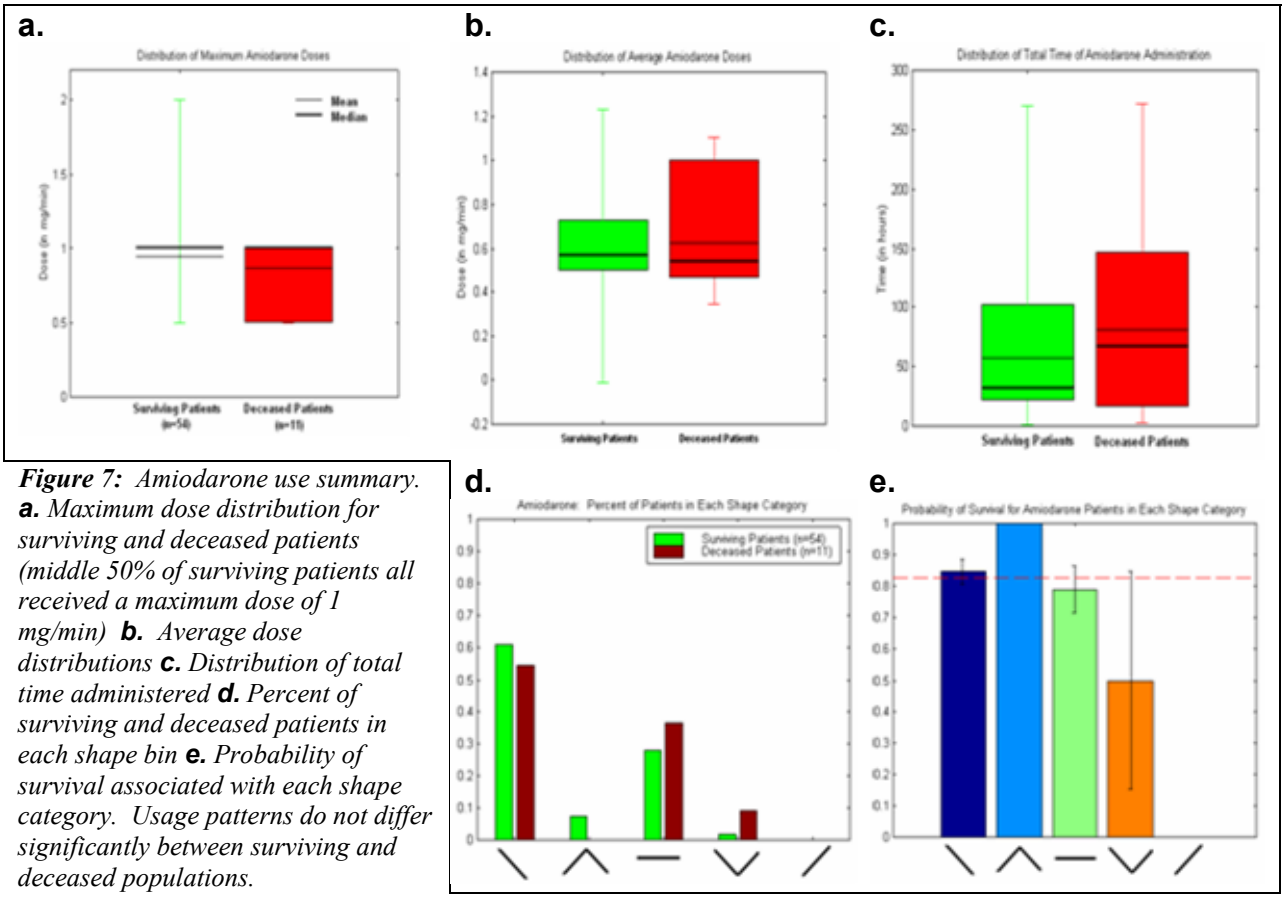


Figure 7: *Amiodarone use summary.* ***a.*** *Maximum dose distribution for surviving and deceased patients (middle 50% of surviving patients all received a maximum dose of 1 mg/min)* ***b.*** *Average dose distributions* ***c.*** *Distribution of total time administered* ***d.*** *Percent of surviving and deceased patients in each shape bin* ***e.*** *Probability of survival associated with each shape category. Usage patterns do not differ significantly between surviving and deceased populations.*

3.2.1.2 Heparin

Heparin [7] is an anticoagulant given to treat or prevent thrombosis (blood clotting). Generally, when the drug is given intravenously, the latter is the case. Typical initial dose for continuous IV Heparin administration is 5000 units, followed by a maintenance dose of 20,000 to 40,000 units over a 24 hour period (approximately 800 to 1600 units/hour). Patients can be on Heparin continuously for many days, and in some cases anticoagulation may continue using oral medications. Heparin dose is adjusted to achieve a desired level of anticoagulation, and is not dependent on underlying pathology. The patterns of use between deceased and surviving patient populations should therefore be similar.

Two hundred cases of intravenous Heparin administration were found to characterize use in the ICU. This corresponds to approximately 20% of the MIMIC II population (200/955). Nineteen of these patients died in the unit, or about 10% of Heparin recipients. Two-sample, two-tailed *t* tests confirm that maximum dose, average dose and administration time are not significantly different between surviving and deceased patients (α=0.05, P_{max}=0.76, P_{ave}=0.62, P_{time}=0.15), as is suggested by Figures 8a-c. Figure 8d indicates that there is no systematic trend in characteristic shapes of Heparin administration for either the deceased or surviving populations. Finally, Figure 8e shows that the probability of survival for Heparin patients in most shape categories is close to that of the overall population of patients receiving Heparin. The reason for the lower probability of survival associated with the "decreasing" shape category is unclear; any physiological explanation for this unexpected result would be purely speculative.

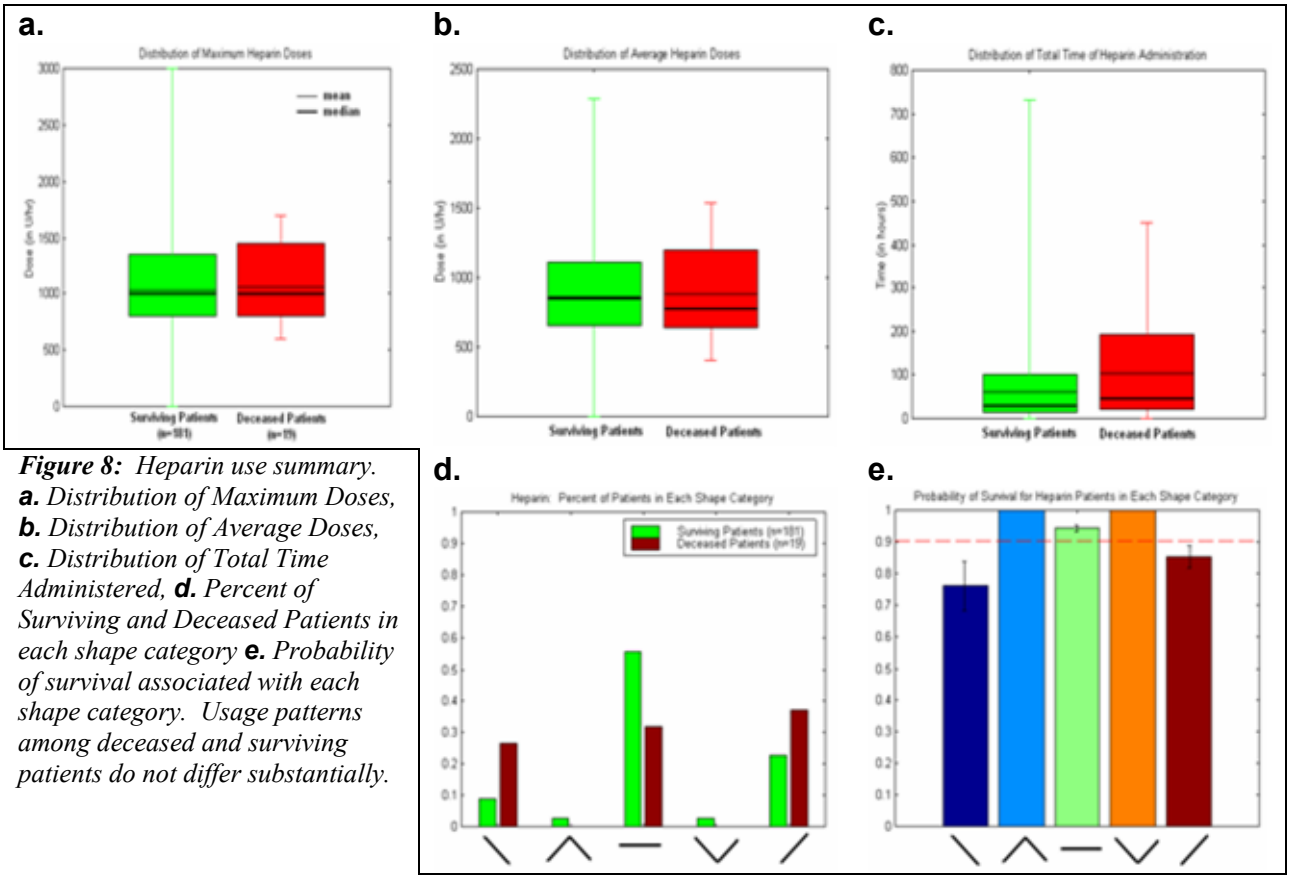


Figure 8: *Heparin use summary.* ***a.*** *Distribution of Maximum Doses,* ***b.*** *Distribution of Average Doses,* ***c.*** *Distribution of Total Time Administered,* ***d.*** *Percent of Surviving and Deceased Patients in each shape category* ***e.*** *Probability of survival associated with each shape category. Usage patterns among deceased and surviving patients do not differ substantially.*

3.2.1.3 Lasix

Lasix [3, 8] is a potent diuretic given to treat the fluid buildup that occurs as a result of conditions such as congestive heart failure, cirrhosis of the liver, or renal disease. Lasix is administered with a continuous IV drip only in cases where frequent large doses are required; one would assume these correspond to patients in very critical conditions. Medical literature indicates that typical bolus Lasix doses range from 20 to 40 mg and can be as high as 80 mg, given every 6 to 8 hours. Typical intravenous doses range from 20 to 40 mg/hr, with a maximum safe administration rate of 4 mg/min (96 mg/hr).

Only 39 cases of IV Lasix administration were found in the database (4% of total population), and of these 28% died in the unit (11/39). These numbers coincide with the expectations for IV Lasix recipients mentioned in the previous paragraph – critically ill patients who require frequent and large doses of the drug. Figure 9 summarizes the use of IV Lasix based on the 39 cases found. Two-sample, two-tailed *t* tests show that maximum dose and administration time are not significantly different between the two populations (α=0.05, P_{max}=0.12, P_{time}=0.06), while average doses are lower among surviving patients (α=0.05, P_{ave}=0.03). Figure 9d shows that the deceased patient cases tend to sort into characteristic shapes toward the right side of the graph, which are thought to correspond to worse patient states. However, it is difficult to separate deceased from surviving cases using only this mechanism. Figure 9e shows the probability of survival for patients sorted into each shape category. Patients receiving decreasing doses toward the end of IV Lasix administration have higher probability of survival than other recipients.

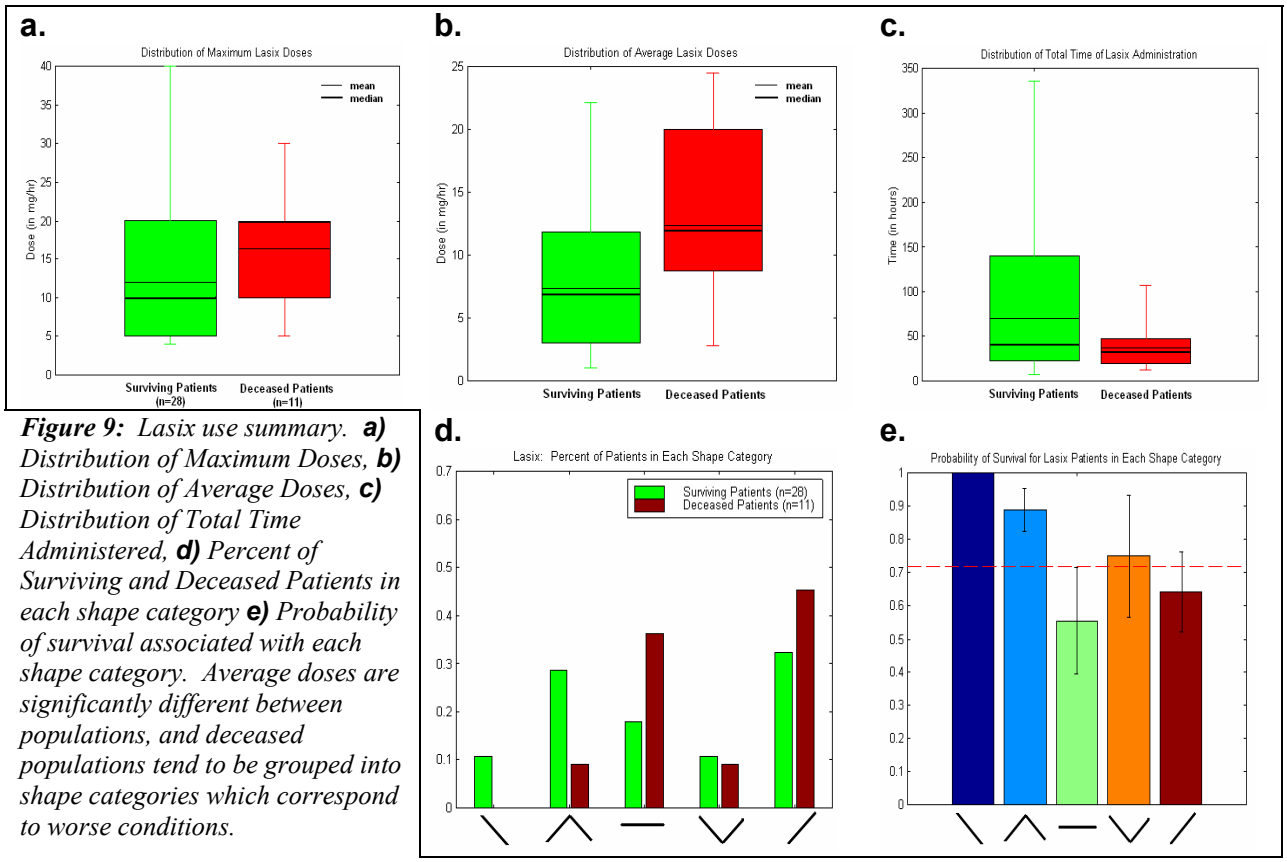


Figure 9: *Lasix use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival associated with each shape category. Average doses are significantly different between populations, and deceased populations tend to be grouped into shape categories which correspond to worse conditions.*

3.2.1.4 Propofol

Propofol [10] is an anesthetic; its use in the ICU indicates that the patient required sedation during ventilation. Typical dose rate is 0.3 to 4.0 mg/kg/hr (50 to 70 µg/kg/min). Two hundred fifty two (252) cases of Propofol administration were found in MIMIC II, or 26% of the patient population. Twelve percent (30/252) of these cases died in the unit. Because response to the sedative is not dependent on overall patient state, is not expected that usage patterns should differ significantly between populations of surviving and deceased patients. Figure 10a-e shows the results of Propofol usage characterization. Two-sample, two-tailed *t* tests show that maximum dose, average dose, and administration time are not significantly different between the two

populations, though maximum dose barely fails the test of significance (α=0.05, P_{max}=0.05, P_{ave}=0.17, P_{time}=0.27). Characteristic shape patterns between surviving and deceased populations are quite similar, and Figure 10e shows that the probabilities of survival associated with each shape category are approximately equal.

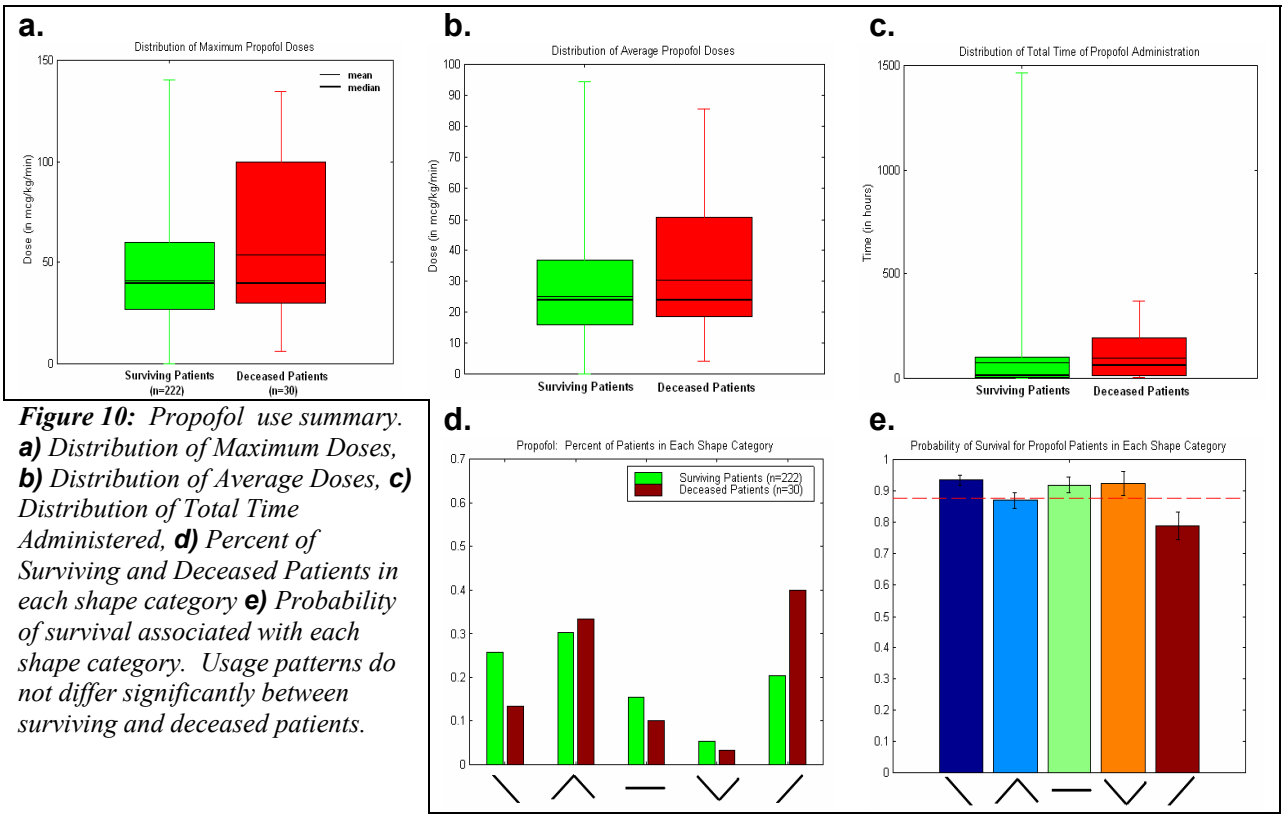


Figure 10: *Propofol use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival associated with each shape category. Usage patterns do not differ significantly between surviving and deceased patients.*

3.2.2 Positive Inotropic Agent Use Characterization

Positive inotropic agents are those which stimulate heart muscle, causing the heart to beat with more force. They are used in cases of systolic heart failure, where cardiac output is severely decreased.

3.2.2.1 Dobutamine

Dobutamine [5] works by stimulating β-receptors in the heart, and as a β-receptor agonist it also causes mild vasodilation in arteries and veins, reducing cardiac afterload and making it easier for the heart to eject blood. It is because of this dual effect that *The ICU Book* calls Dobutamine "the drug of choice for acute management of severe systolic heart failure." Typical doses are in the 5 to 15 μg/kg/min range, but the response in critically ill populations is highly variable and the dose is guided by patient response rather than predetermined dose rates.

Forty-one cases of Dobutamine administration were found in MIMIC II, or approximately 4% of the total population. Twenty-nine percent (12/41) of these patients died in the unit. Figure 11 shows that usage patterns are nearly identical between surviving and deceased patients given Dobutamine. Average and maximum doses generally fall within the 5 to 15 μg/kg/min range suggested in the literature and most patients receive the drug for less than 4 days (96 hours).

Two-sample, two-tailed *t* tests show that maximum dose, average dose, and administration time are not significantly different between the two populations (α=0.05, P_{max}=0.88, P_{ave}=0.90, P_{time}=0.66). Figure 11d is interesting in that 1/3 of deceased patients fall into the "decreasing then increasing" category while none of the surviving population does. Conversely, there are no deceased cases in the "increasing then decreasing" category. Figure 11e shows that the probability of survival for the other three shape patterns closely matches the overall probability of survival for patients given Dobutamine.

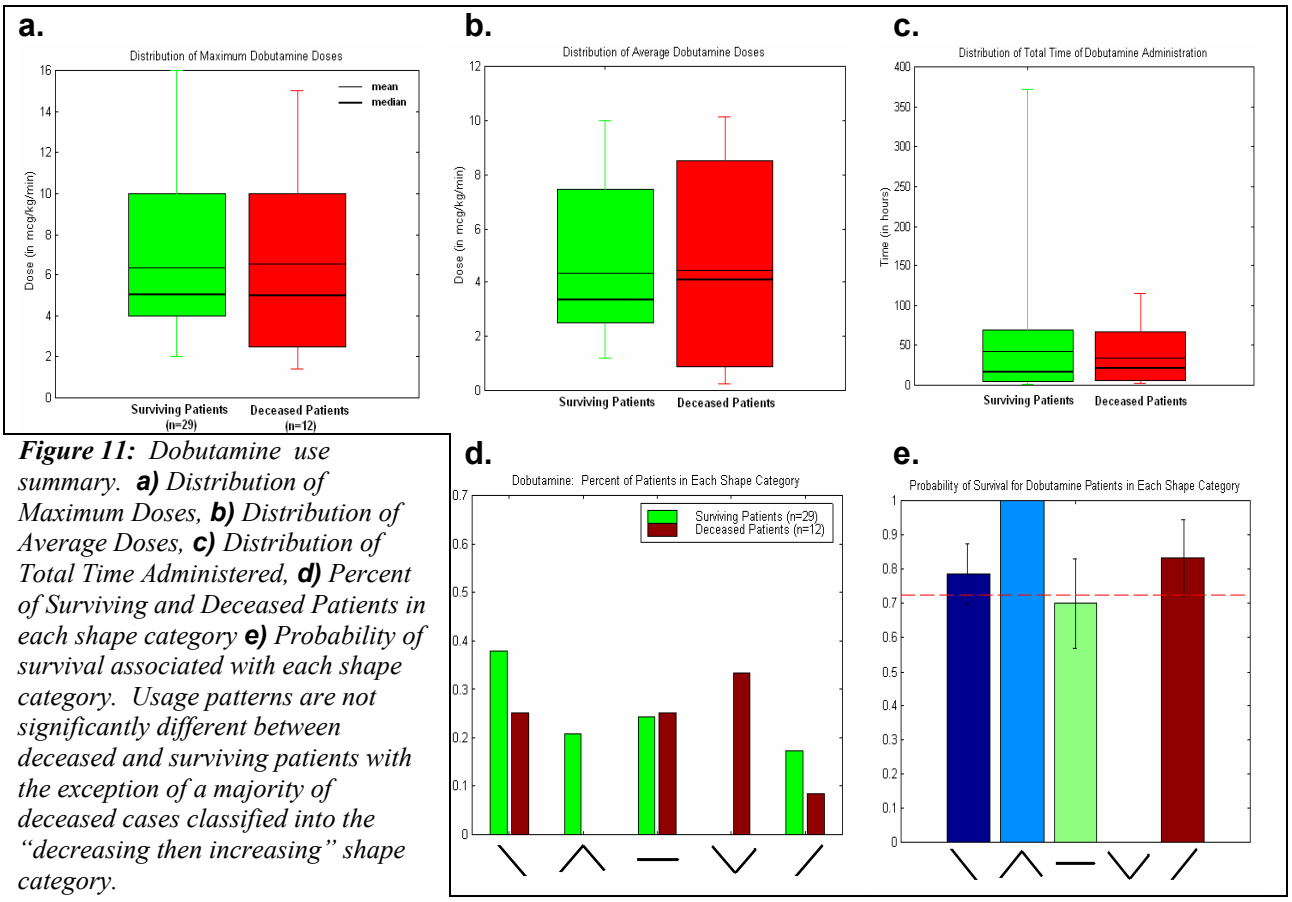


Figure 11: *Dobutamine use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival associated with each shape category. Usage patterns are not significantly different between deceased and surviving patients with the exception of a majority of deceased cases classified into the "decreasing then increasing" shape category.*

3.2.2.2 Milrinone

Milrinone [3, 4] also falls into the positive inotrope category, but it works by inhibiting cAMP in cardiac and vascular muscle, rather than by stimulating β-receptors. The effects are similar to Dobutamine: increased contractility and vasodilation. It is indicated for use in treating congestive heart failure. Loading dose is around 5 μg/min for 10 minutes followed by typical maintenance doses in the 0.26 to 1 μg/kg/min range.

Forty-eight cases of Milrinone administration were found in MIMIC II (about 5% of patients), and 11% of these died in the unit (5/48). Figure 12 summarizes the use of Milrinone. Doses fall within the 0.26 to 1 μg/kg/min guidelines (Figure 12a-b). Two-sample, two-tailed *t* tests show that there is a significant difference in maximum and average doses between deceased and surviving patients (α=0.05, P_{max}=0.002, P_{ave}=0.05), while administration time did not differ significantly between the two groups (α=0.05, P_{time}=0.32). Figure 12d shows that surviving

patients tend to fall into categories on the left side of the plot, which typically indicate improving states toward the end of drug administration; deceased cases do not show this tendency. Few conclusions can be drawn in categorizing the deceased population in this way, due to the small number of patients in this group. For this reason, probability of survival for each shape category is not shown.

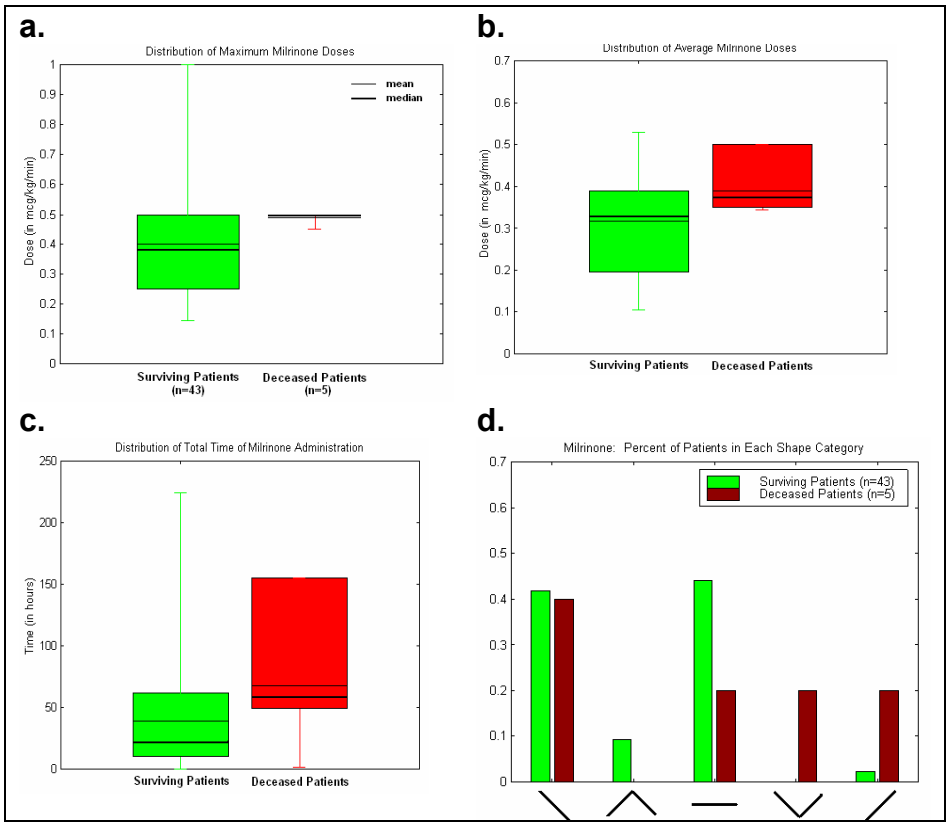


Figure 12: *Milrinone use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category. Maximum and average doses were significantly different between the two groups.*

3.2.3 Vasodilator Use Characterization

Vasodilators act to relax smooth muscle surrounding veins and arteries, increasing flow through these vessels and deceasing blood pressure. The two drugs considered here both fall into the category of nitrovasodilators, which means that they work when nitrous oxide (NO) moves into the smooth muscle surrounding blood vessels and promotes a chemical reaction which produces vasodilation.

3.2.3.1 Nitroglycerine

Nitroglycerine is often administered to control chest pain in cases of myocardial infarction (MI). The vasodilation caused by Nitroglycerine decreases cardiac afterload and increases blood supply through coronary arteries, reducing the workload of the heart. These effects occur very soon after beginning Nitroglycerine administration and last for a short time without continuous administration. Nitroglycerine doses are typically in the 5 to 50 μg/min range. Tolerance to Nitroglycerine can occur, so the drug is typically discontinued for 6-8 hours each day.

Nineteen percent (185/955) of MIMIC II cases included Nitroglycerine administration, with 4% (7/185) of these cases from patients who died in the ICU. Figure 13a-c shows that there is little

difference in maximum dose, average dose, or length of time administered between deceased and surviving populations of Nitroglycerine recipients. Two-sample, two-tailed *t* tests confirm this observation (α=0.05, P_{max}=0.62, P_{ave}=1.0, P_{time}=0.41). Figure 13d shows that surviving cases tend to be sorted into categories on the left side of the graph, but there is significant overlap in shape patterns between deceased and surviving populations. Figure 13e shows that the probability of survival is slightly lower than average for patients in shape categories which increase toward the end of drug administration. These increasing doses may indicate persistent or recurrent chest pain which is common in cases of coronary disease or MI, though it is difficult to confirm whether this is the case since underlying pathology is not included in MIMIC II.

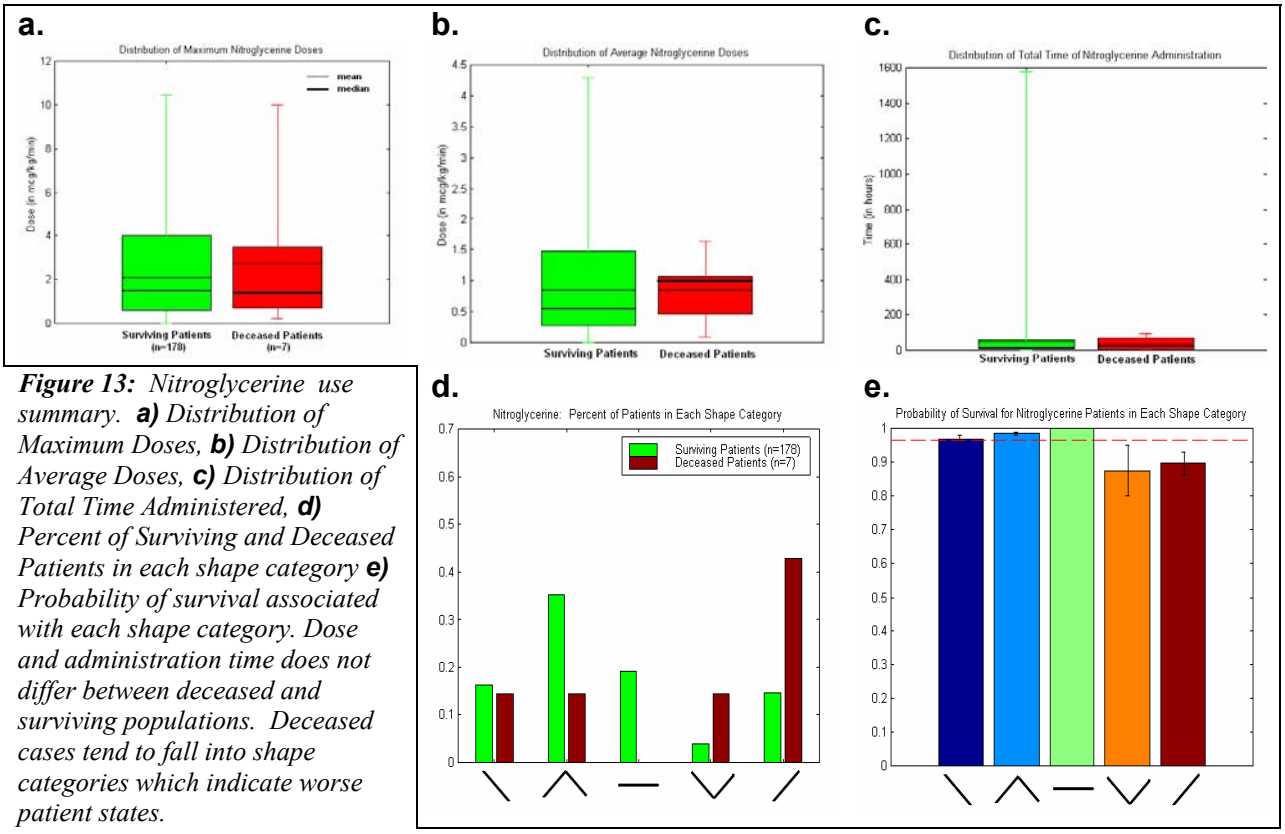


Figure 13: *Nitroglycerine use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival associated with each shape category. Dose and administration time does not differ between deceased and surviving populations. Deceased cases tend to fall into shape categories which indicate worse patient states.*

3.2.3.2 Nitroprusside

Nitroprusside [5] effects are similar to those of Nitroglycerin, however the medical literature indicates that it is an extremely dangerous drug because it promotes cyanide accumulation if administered for long periods. Typical dose range is 0.5 to 2 µg/kg/min, with the absolute maximum dose being 10 µg/kg/min for no more than 10 minutes. It is used to treat cases of severe hypertension combined with low cardiac output.

Because of its potential toxicity, it is not surprising that there are fewer cases of Nitroprusside administration than Nitroglycerine. Sixty-three cases of Nitroprusside administration were found, and only one of these patients died in the unit. Because there was not a large enough population to characterize use among deceased patients, the summary plots have been combined (Figure 14a-c) and tests of significance were not performed. Figure 14a-b show that the Nitroprusside doses typically fall within the guidelines, and total administration time is generally

under 100 hours. There are, however, surprising outliers. Figure 14d indicates that the most common pattern of administration is "increasing then decreasing," as would be expected from a drug which is typically titrated until the desired patient response is seen, then weaned off once the patient state improves. As with Nitroglycerine, the pattern of use seems to indicate a drug whose administration is either 1) not indicative of a patient condition in which a negative outcome is likely, or 2) extremely effective in treating and stabilizing conditions for which its use is indicated.

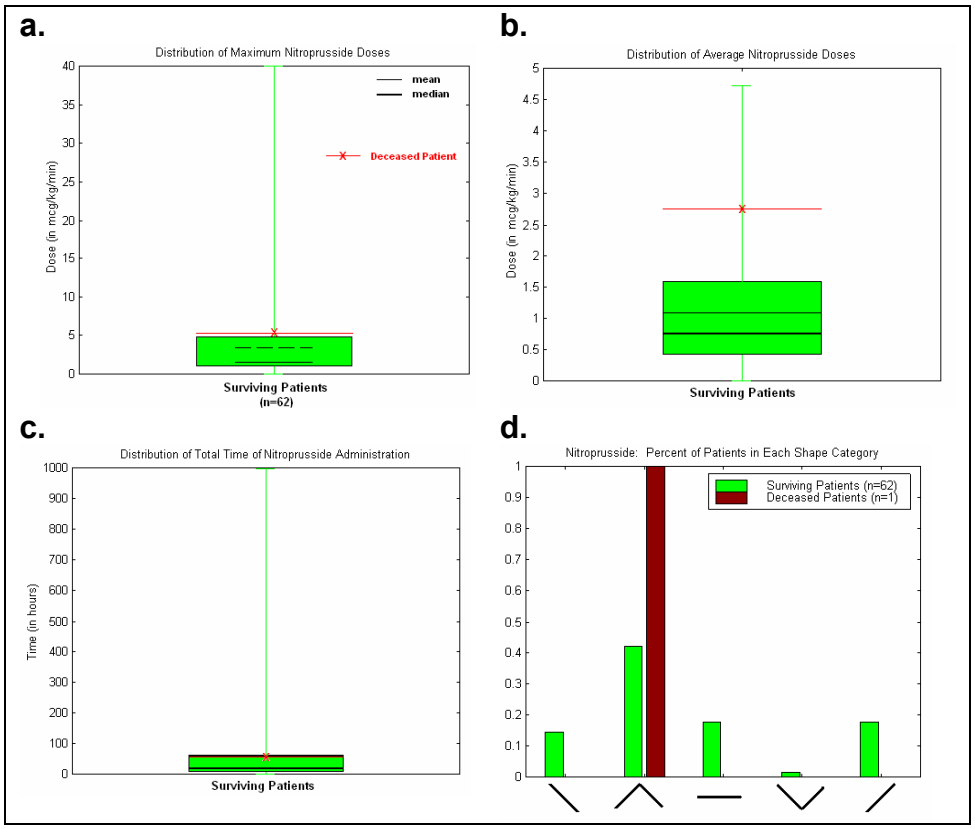


Figure 14: *Nitroprusside use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category.*

3.2.4 Vasoconstrictor Use Characterization

Vasoconstrictors work by tensing smooth muscle surrounding blood vessels. They are generally administered to treat hypotension, which may range from moderate to severe, such as occurs in cases of shock or shock-like states. In these cases, blood pressure is dangerously low and blood flow is inadequate to the vital organs. Administration of vasoconstrictors causes an increase in blood pressure and promotes adequate perfusion of vital organs by decreasing blood flow to the periphery. The use of vasoconstrictors comes with an important tradeoff. In maintaining adequate flow to the heart and brain, it is possible to damage the kidneys or liver because constriction has reduced blood flow to these regions. Additionally, the heart has to pump harder to maintain adequate blood supply during vasoconstriction. In the critically ill population of the ICU, this is an especially important consideration. Because these drugs have potentially very dangerous effects, their use can indicate very critical patient conditions in which other treatment options are not available.

3.2.4.1 Dopamine

Dopamine [5] is unique in the class of vasoconstrictors in that its vasoconstrictive effects do not occur at all dose levels. In low doses (less than 3 μg/kg/min), Dopamine administration stimulates dopamine receptors in the renal, mesenteric, and cerebral systems, increasing blood flow to these areas. In intermediate doses (3 to 7.5 μg/kg/min), Dopamine also activates β-receptors and produces a modest inotropic response (see Section 3.3). In high doses, (greater than 7.5 μg/kg/min), Dopamine activates α-receptors and the vasoconstrictive effects described above predominate. Typical doses are in the 2 to 20 μg/kg/min range, with a maximum safe dose of 60 μg/kg/min.

Approximately 15% of the cases in MIMIC II include Dopamine administration (139/955), and nearly one quarter of these come from patients who died in the unit (34/139). Figure 15 reveals that Dopamine recipients primarily received high doses (greater than 7.5 μg/kg/min), which produce vasoconstriction. Both maximum and average doses are well below the 60 μg/kg/min limit, and it appears that deceased patients require higher doses than those that survive. Two-sample, two-tailed *t* tests confirm this observation (α=0.05, P_{max}=0.008, P_{ave}=0.008). Length of time administered does not differ significantly between the two groups (α=0.05, P_{time}=0.350). Figure 15d shows that the surviving patients tend to be grouped into categories on the left side of the graph, which are assumed to indicate improving state toward the end of administration. Deceased patients show no such tendency to cluster; there is quite a bit of similarity in the patterns of use among deceased and surviving patients. However, Figure 15e makes it clear that patients who require increasing doses of Dopamine toward the end of the record have significantly decreased probability of survival compared to other Dopamine recipients.

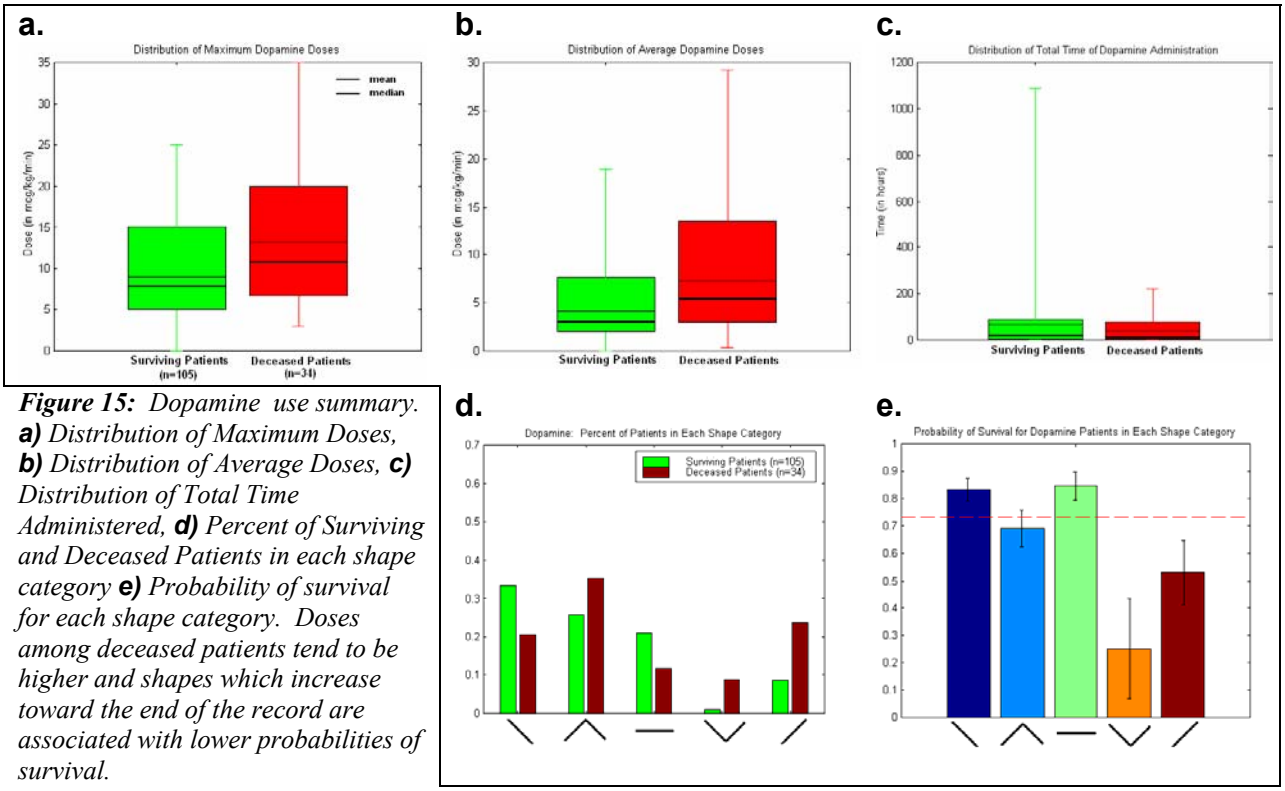


Figure 15: *Dopamine use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival for each shape category. Doses among deceased patients tend to be higher and shapes which increase toward the end of the record are associated with lower probabilities of survival.*

3.2.4.2 Levophed

Levophed [5] is indicated for use in acute hypotensive states, which might occur due to heart attack, sepsis, drug reactions, or blood loss. It is not generally a first-line drug for treatment of circulatory shock; however, it is often added in these cases after Dopamine or Neosynephrine have failed to be effective. As with these other drugs, the primary effect of Levophed is peripheral vasoconstriction. The typical dose range for Levophed is 0.03-0.6 µg/kg/min [5].

One-hundred thirty-three cases of Levophed administration were found in MIMIC II (14%) and 31% of these come from patients who died in the unit (39/133). The patterns of use for Levophed look very similar to those of Dopamine, which is not surprising given the common indications and drug effects. Like Dopamine, deceased patients seem to require larger doses of the drug to maintain adequate blood pressure (Figure 16a-b) and two-tailed t tests confirm this observation (α=0.05, P_{max}=0.002, P_{ave}=0.000). Length of time administered (Figure 16c) does not significantly differ between deceased and surviving patients (α=0.05, P_{time}=0.680). The shape characterization shown in Figure 16d is quite similar to that of Dopamine, though Levophed populations show an even more pronounced tendency to cluster toward the left, in the case of survivors, and somewhat to the right, in the case of deceased patients. Figure 16e shows a probability of survival trend even more severe than that of Dopamine; those patients decreasing or flat categories have very high probabilities of survival while those with increasing doses toward the end of the record have very low probabilities of survival. "Increasing then decreasing" is the most common pattern of drug administration, as would be expected for a drug which is titrated until desired response is seen, then weaned once patient state improves. It can be seen that patients in this category have a probability of survival which matches that of the overall population of Levophed recipients.

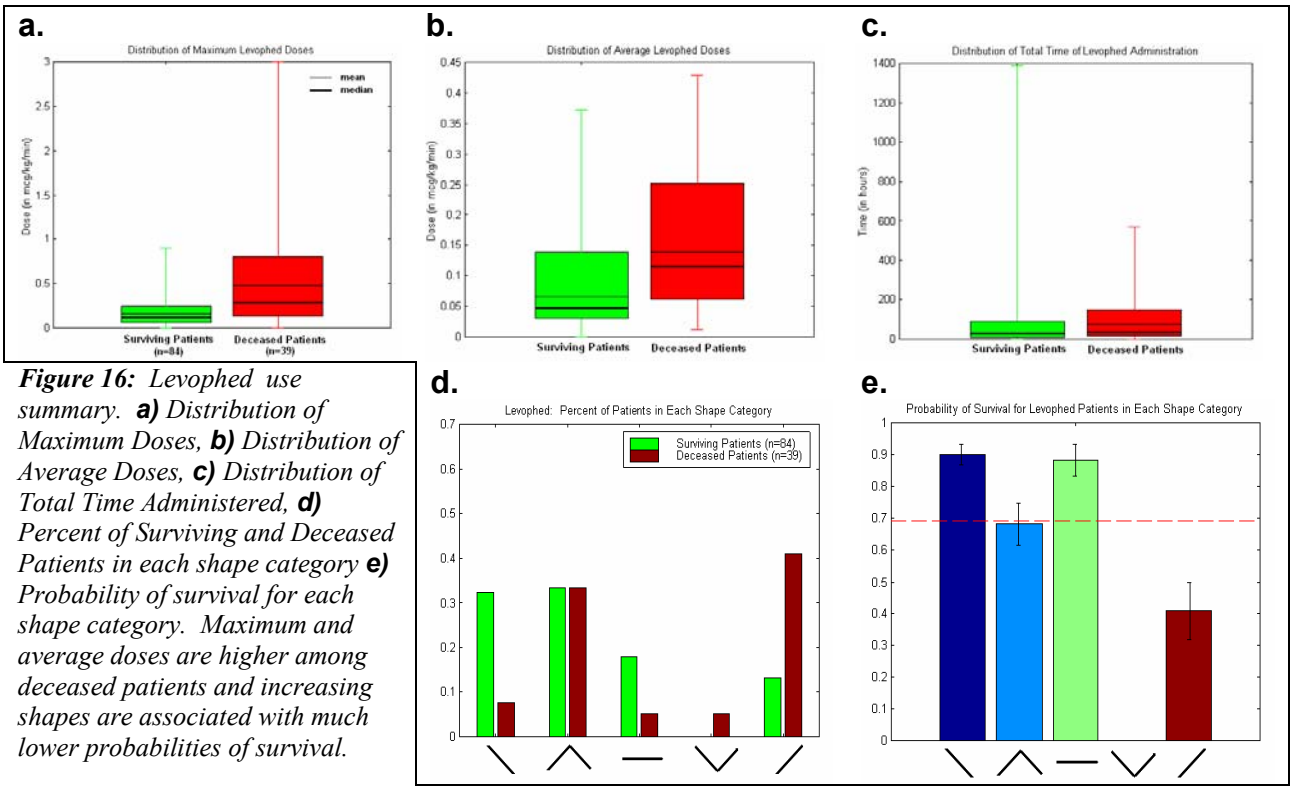


Figure 16: *Levophed use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival for each shape category. Maximum and average doses are higher among deceased patients and increasing shapes are associated with much lower probabilities of survival.*

3.2.4.3 Neosynephrine

Like the other vasoconstrictors, Neosynephrine [3, 9] is used in the ICU in the treatment of hypotension. Neosynephrine has properties very similar to Levophed, but has several advantages over that drug including longer-lasting effects and a reduced incidence of arrhythmias. Initial dose range for Neosynephrine is 100 to 180 μg/min, while maintenance doses range from 40 to 60 μg/min.

One hundred ninety-three cases of Neosynephrine administration were found in MIMIC II (20%), with 21% of these cases dying in the unit (41/193). Like the other vasoconstrictors, deceased patients on Neosynephrine received significantly higher doses than survivors (Figure 17a-b, two-tailed t test α=0.05, P_{max}=0.012, P_{ave}=0.000). Length of time on Neosynephrine are not significantly different between the two groups (α=0.05, P_{time}=0.340). Shape patterns for Neosynephrine are similar to Dopamine and Levophed, with surviving patients clustered in categories on the left side of the graph. Deceased patients show no such tendency to cluster, though the "increasing" category is dominated by patients who died in the unit. Figure 17e shows that the probability of survival in this category is significantly lower than for patients in the other four categories.

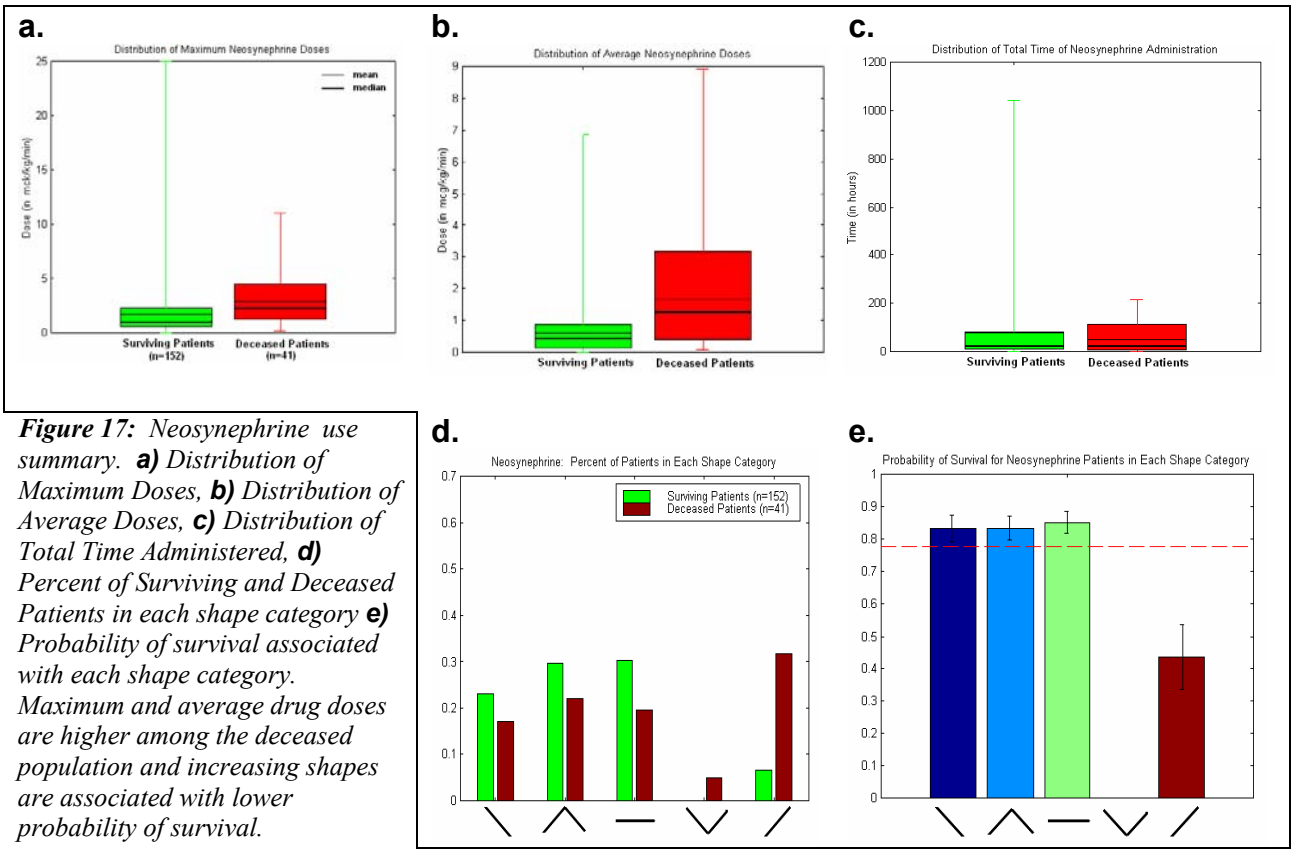


Figure 17: *Neosynephrine use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival associated with each shape category. Maximum and average drug doses are higher among the deceased population and increasing shapes are associated with lower probability of survival.*

3.2.4.4 Vasopressin

Vasopressin [11, 12] is an antidiuretic hormone which also stimulates smooth muscle surrounding blood vessels, resulting in vasoconstriction. It is indicated for the "prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel

interfering gas shadows, and in diabetes insipidus." Its use in intensive care is relatively rare, and generally indicates severe cases such as septic shock or upper GI bleeds. Typical doses for IV Vasopressin administration in the ICU population range from 0.2 to 2.0 μg/min.

Thirty-nine cases of Vasopressin administration were found in MIMIC II, or 4% of the patient population. Almost half of these patients died in the unit (19/39), consistent with its use in only the most critical cases. Figure 18a-b suggests that deceased patients may require higher doses of the drug to achieve the desired physiological response, however two-tailed *t* tests reveal that this difference is not significant (α=0.05, P_{max}=0.190, P_{ave}=0.120, P_{time}=.586). The patterns of used revealed in the shape characterization shown in Figure 18d are very similar between deceased and surviving populations, with the exception of the "increasing" category which is dominated by patients who died in the unit. Figure 18e shows that the probability of survival for patients in this group is very low, while patients in other groups have a probability of survival equal or better than that of average Vasopressin recipients. It is interesting to note that unlike the other vasoconstrictors considered, Vasopressin does not appear to be associated with a titrating/weaning pattern. These results paint a picture of a drug whose use is very different from other vasoconstrictors. The results suggest that this drug is used in only the most severe cases, perhaps as a last resort when other drugs have failed to produce the desired patient response.

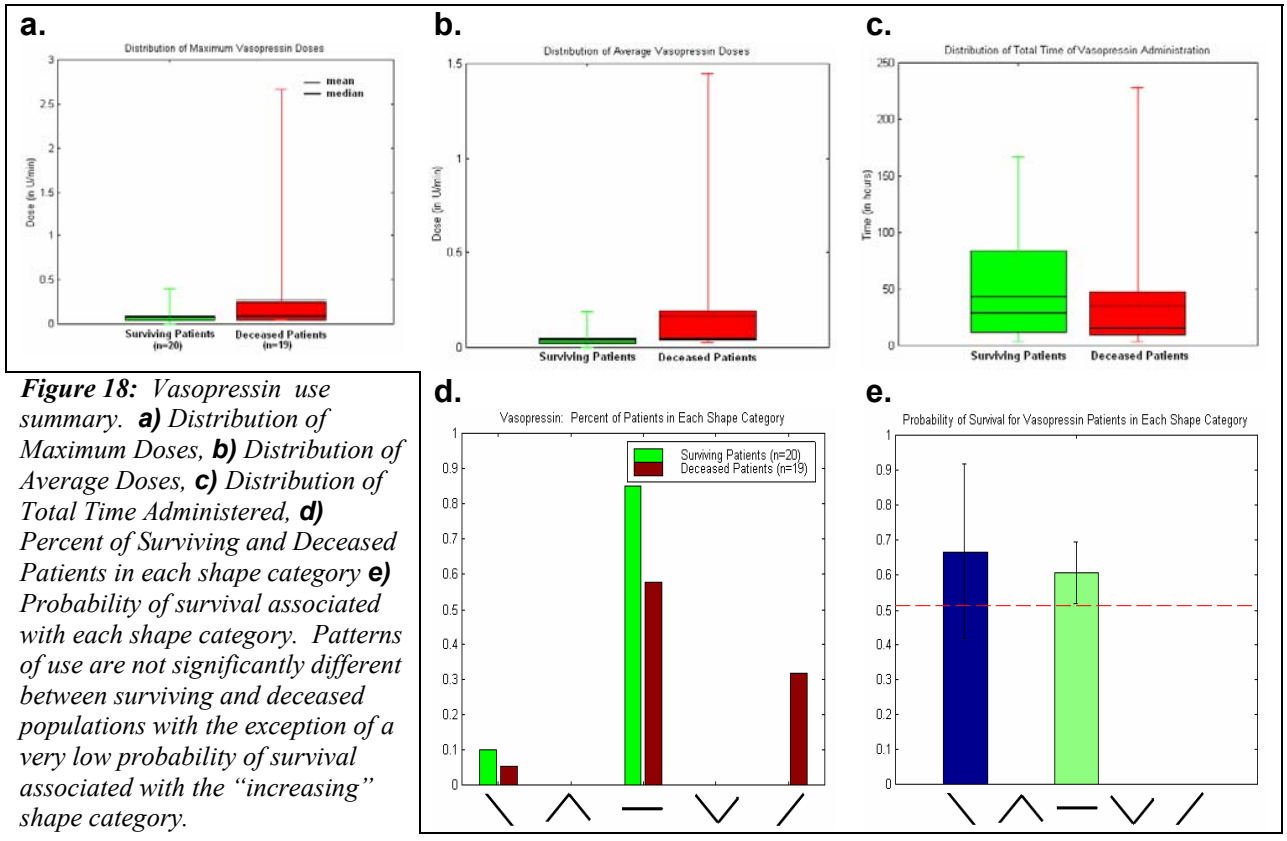


Figure 18: *Vasopressin use summary.* ***a)*** *Distribution of Maximum Doses,* ***b)*** *Distribution of Average Doses,* ***c)*** *Distribution of Total Time Administered,* ***d)*** *Percent of Surviving and Deceased Patients in each shape category* ***e)*** *Probability of survival associated with each shape category. Patterns of use are not significantly different between surviving and deceased populations with the exception of a very low probability of survival associated with the "increasing" shape category.*

4 Visualizing Drug Dose versus Mean Blood Pressure Response

In the ICU, it is important to track the progress of a patient's state, i.e. to know whether the patient is better today than he was yesterday. When vasoactive drugs are administered, one of the most important indicators of overall patient state is mean blood pressure. Dose information and blood pressure are both recorded over the course of a patient's stay, but synthesizing the two trends and how they relate to each other is difficult for a human to do rapidly. The relationship of these two trends contains important information, and the goals of comparing these trends are similar to those of the advanced patient monitoring algorithms described in Section 1.2: assessment of current patient response, prediction of future response and quantification of the "distance" from a target response.

4.1 Viewing Dose and Mean Blood Pressure Time Series

The easiest and most intuitive way to view both mean blood pressure and drug dose is as a straight time series. Figure 19 shows what a display of the two trend plots might look like. Target blood pressure is indicated by a shaded region in the top graph. In this example, it is easy to see that as the Levophed dose increases, the blood pressure continues to drop, indicating that the patient is not responding well to the drug. While intuitive, this method does not provide a way of quantifying patient response more precisely.

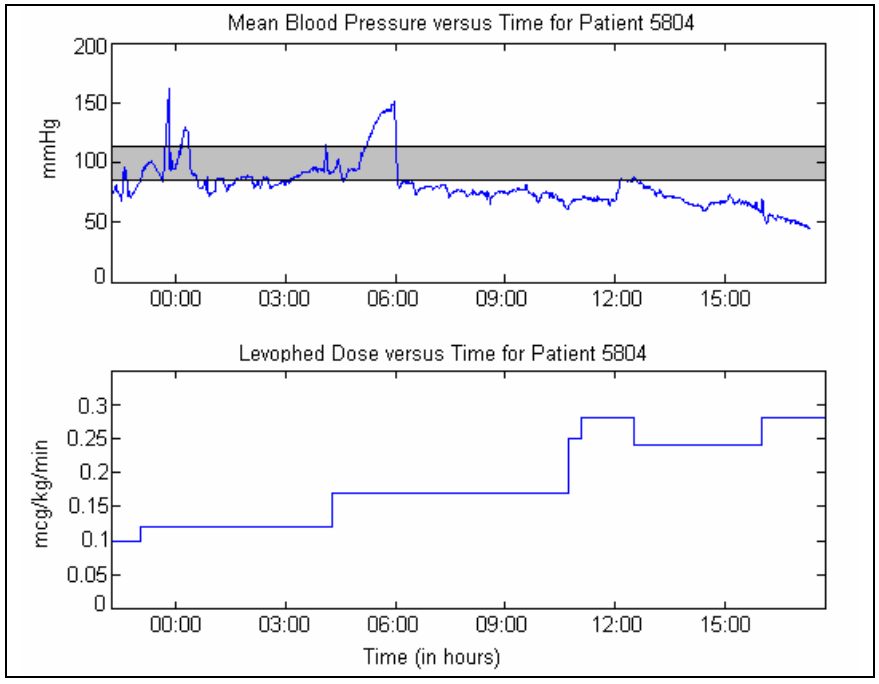


Figure 19. *Sample display comparing trend plots of mean blood pressure and drug dose.*

4.2 Viewing 2-D Representation of Blood Pressure vs. Drug Dose

To more precisely capture a patient's response to a drug over time, mean blood pressure was plotted as a function of drug dose over the course of the patient's stay. Figure 20 shows such a 2-dimensional representation of this information, using the same example presented in Figure 19. For each charted dose, blood pressure was found by taking the median of available measurements from 10 minutes before to 20 minutes following time of dose recording. Time

information is captured imprecisely by different-colored indicators. Triangles function as arrows which indicate whether the next dose is associated with a higher or lower blood pressure.

Plotting blood pressure versus dose in this manner allows easy quantification of patient response. The slope of the curve indicates how sensitive the patient is to Levophed, a large increasing slope would indicate high sensitivity, while a negative slope such as the one in Figure 20 indicates that the patient is not responding well. In addition to quantifying sensitivity, this method allows identification of graph regions which indicate comparatively better or worse patient states. Solid black lines on the display indicate the range of normal mean blood pressure as well as low, intermediate, and high dose ranges. A trajectory which includes primarily low drug doses and stable, normal blood pressures indicates a better patient state than one such as the example shown in Figure 20 where blood pressure is very low despite very high doses.

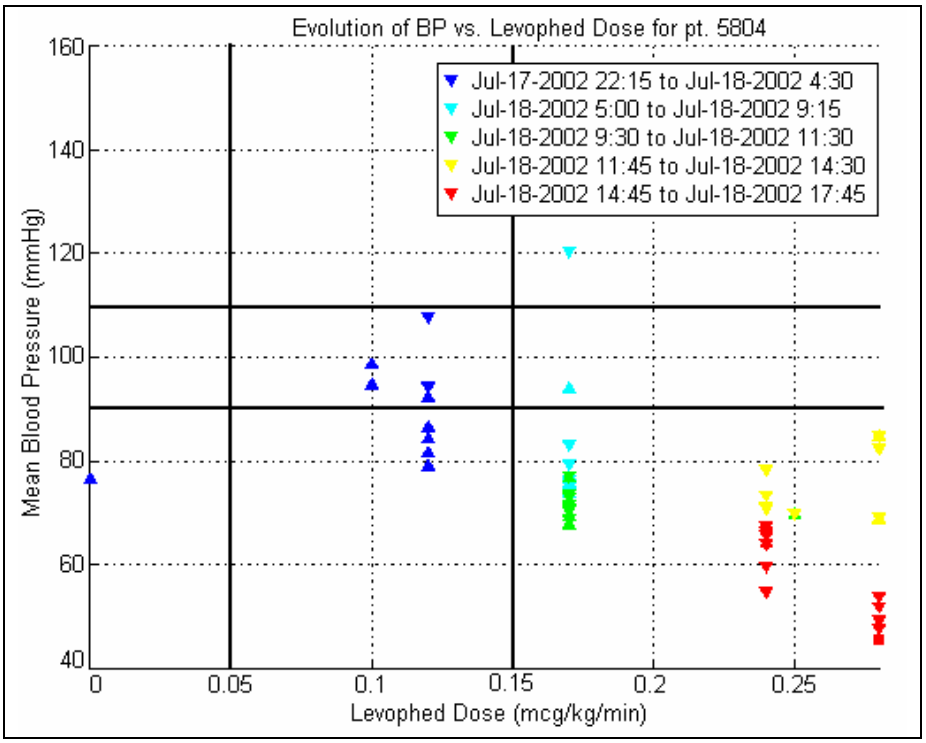


Figure 20. *Blood pressure response as a function of drug dose. Solid black lines indicate normal range of mean blood pressure and low, intermediate, and high dose ranges for Levophed. Arrows indicate whether the blood pressure is increasing or decreasing. For this example, the negative overall slope indicates low sensitivity, while a trajectory in the lower right quadrant indicates a very poor patient state.*

The major drawback to viewing patient response in this manner is that time information is imprecisely captured. General trends are identifiable, but the stepwise dose functions and the highly variable nature of blood pressure trends make it nearly impossible to mentally reconstruct the time courses of blood pressure or drug dose. This makes more complicated trends than that shown in Figure 20 very difficult to review.

Figure 21 shows a more complicated example of a blood pressure/drug dose relationship. The straight time series comparison provides little insight into this relationship, and the 2-dimensional representation does little better. In the case of the time course comparison, the difficulty lies primarily in reconciling the rapid changes in blood pressure and dose which occur at the beginning of the record. A zooming capability might reduce this problem somewhat, but is unlikely to eliminate the problem of comparing two rapidly-changing trends. In plotting blood pressure versus drug dose, some insight is gained into the patient's sensitivity to Levophed. We

also see that near the end of the record, doses decrease while mean blood pressure remains approximately constant, consistent with a weaning of the drug after a positive patient response. However, in this representation, the frequent increases and decreases in drug dose at the beginning of the record are impossible to reconstruct.

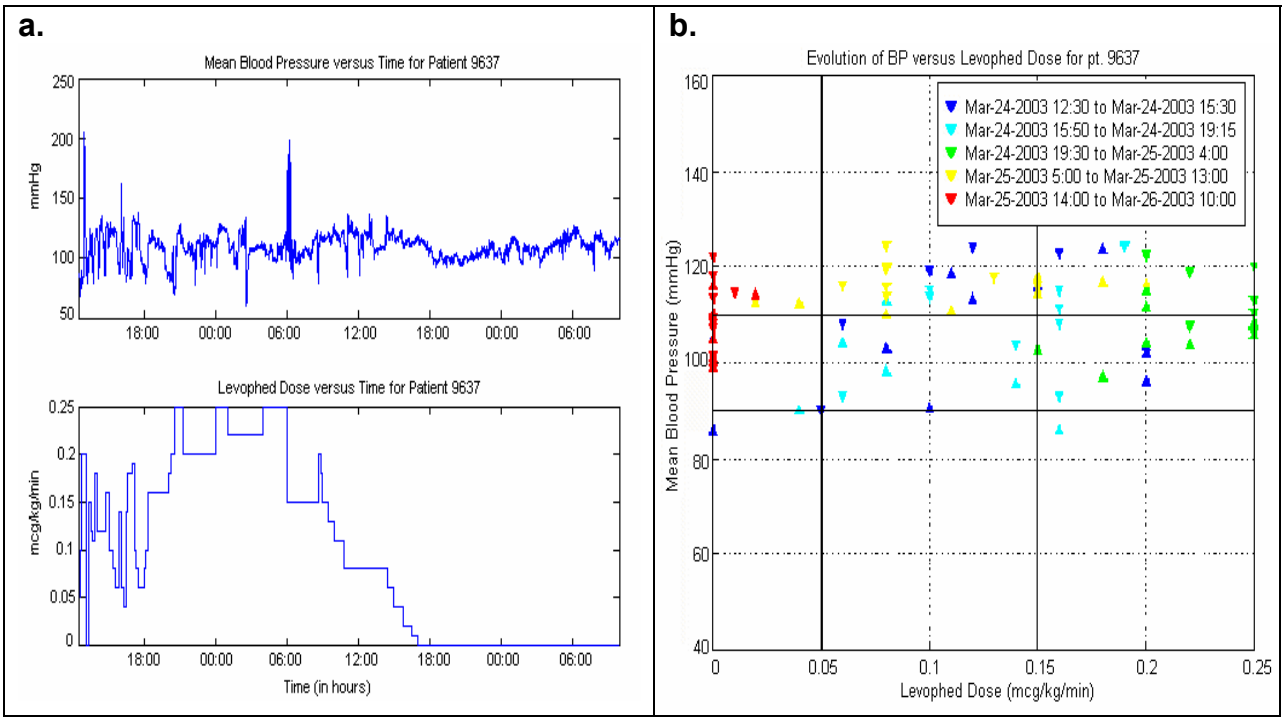


Figure 21. *A more complicated example of blood pressure/drug dose relationship. The rapid increases and decreases in dose at the beginning of the record make both the straight time series (**a**) and the 2-dimensional representation (**b**) inadequate for reconstructing patient response.*

4.3 Viewing 3-D representation of BP vs. Dose Over Time

The difficulty in reconstructing the time courses of the blood pressure and dose trends is decreased by using a 3-dimensional representation to capture time information more precisely. By plotting blood pressure with respect to time in the x-y plane, and drug dose in the z direction, it is possible to gain a clearer picture of current and projected patient response.

Figure 22 shows the simple example from Figures 19 and 20 plotted in this manner. As with the straight time-series comparison, the overall relationship between drug dose and blood pressure response is clearly observable. In this example, mean blood pressure continues to drop despite increasing doses of Levophed. In addition to the long-term patterns, Figure 22 makes it is easier to quantify the transient increases in blood pressure in response to step increases in drug dose.

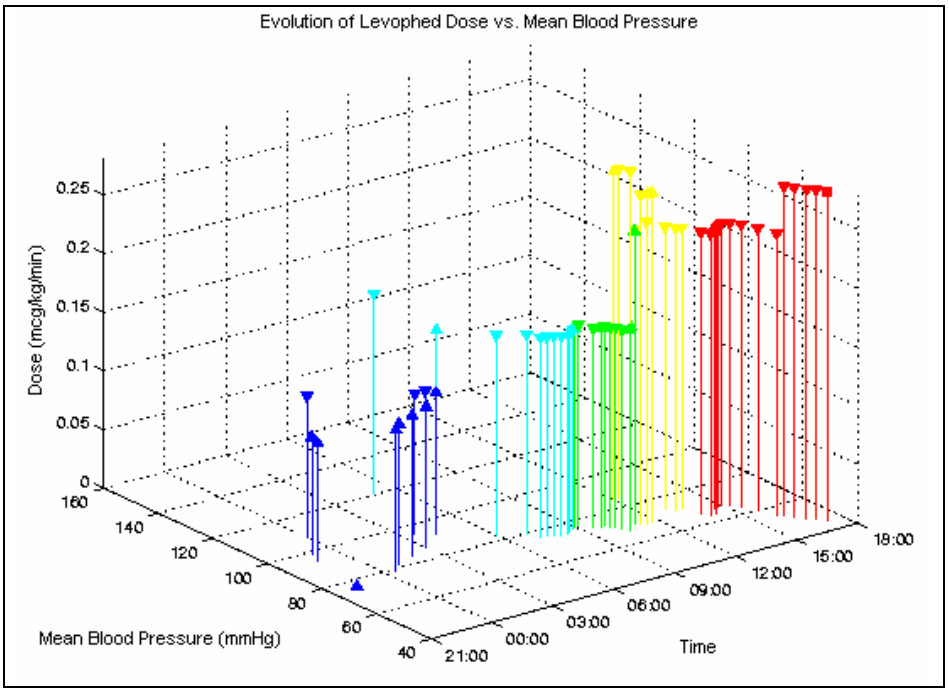


Figure 22. *A 3-dimensional representation of the evolution of blood pressure response to Levophed dose over time. The blood pressure trend is plotted in the x-y plane, while the height of the stems indicates the drug dose at each recorded time. In this example, we see that the patient receives very large drug doses as mean blood pressure continues to drop. The transient blood pressure responses to step increases in dose are also observable in this representation.*

The 3-dimensional representation of blood pressure response to drug dose combines many of the advantages of the simple time series comparison and the 2-dimensional plot of blood pressure versus dose. Some of the detail in the time dimension is lost, and it is more difficult to quickly assess patient sensitivity to a given drug. However, the major drawback of using this method relates to the fact that the more information included in a display, the more attention and training are required before relevant information can be extracted quickly and effectively.

As with the 2-dimensional representation discussed in the previous section, it is straightforward to define a "target response region" for this plot. Normal mean blood pressures range from approximately 90 to 110 mmHg in the normal healthy population. These numbers are probably lower among the ICU population receiving vasoconstrictors, but it is still a simple matter to mark an appropriate range on the x-y plane on the graph. Short stems with bases inside this range would indicate a good patient state, while tall stems with bases in the hypotensive region would indicate a poor patient state. The 3-dimensional representation has the added benefit of providing most of the detailed time information available in the straight time-series plots. This is most important when reconstructing a more complicated record, such as the one originally presented in Figure 21. This record is replotted in Figure 23 using the 3-D stem plot.

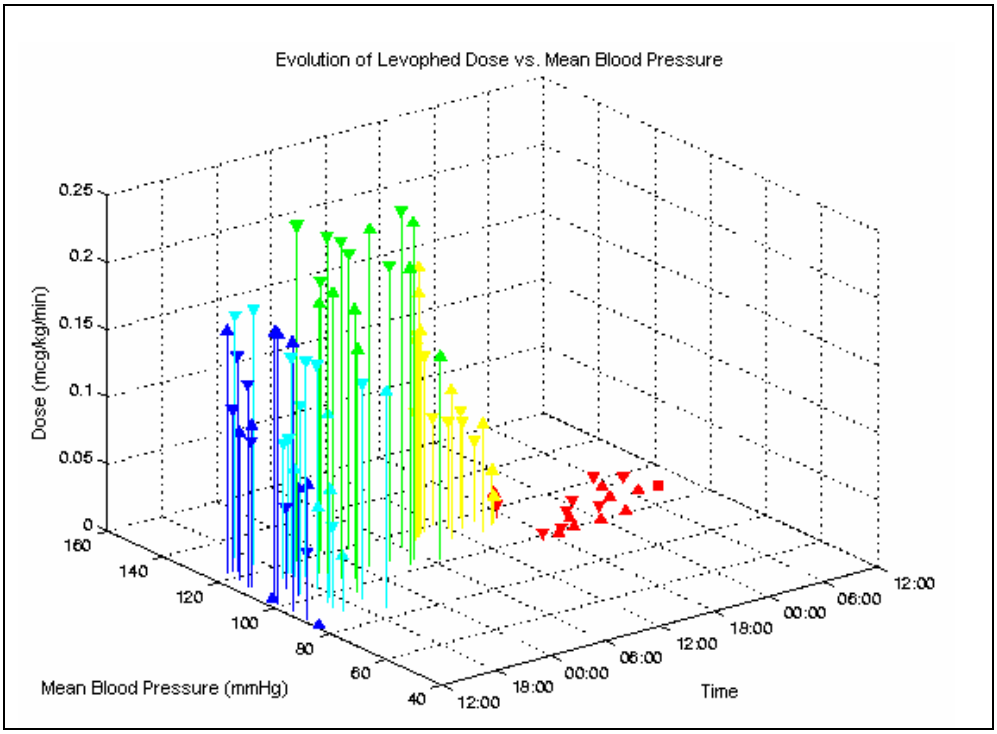


Figure 23. *Three-dimensional representation of the more complicated example originally presented in Figure 22. The many increases and decreases in drug dose and the corresponding blood pressure responses are easier to view using three dimensions .*

5 Conclusions

5.1 Information Extraction from Patient Databases

Development of an effective advanced patient monitoring system depends on comprehensive annotation of MIMIC II. Some method of efficient annotating is necessary to prevent this from becoming an overwhelming task. Ongoing development of an Annotation Workstation aims at providing the necessary filtering and data organization for efficient database annotation. As described in Chapter 2, locating intravenous medication changes in MIMIC II has proven straightforward. Similar methods are employed by the Annotation Workstation to locate not only medication changes, but other diagnostic and therapeutic interventions as well. Once these interventions are located, it is easier to link to other relevant information, such as blood pressure trends or laboratory test results, which may contribute to an assessment of current hemodynamic state and trajectory.

5.2 Characterization of Medication Administration Using MIMIC II

In evaluating the hemodynamic state of a patient, it is necessary to take into consideration many different types of data, including medications administered, blood pressure trends, nurses' progress notes, laboratory test results, and more. By analyzing a subset of this information, it is possible to get one step closer to making such an assessment. The results of drug use characterization presented in Chapter 3 have shown that the pattern of use of some intravenous medications is correlated with patient outcome, an imprecise indicator of overall patient state.

Dose trend features such as maximum dose or length of time administered do not capture all the information needed to characterize drug usage in the ICU. Similarly, characterizing only the

overall shape of the trends provides an incomplete picture of usage patterns. However, combining trend features and overall shape can provide a reasonable characterization of usage patterns for most of the drugs considered. These patterns of use seem to hold not only for single drugs, but for classes of drug as well. For example, with all the vasoconstrictors considered, higher doses were given to patients who died in the unit, presumably because as the health of these patients declined, higher doses were needed to maintain an adequate blood pressure response. The overall shape characterizations also look very similar for these drugs; typically they are titrated until the appropriate response is seen, then weaned off as patient condition improves. Deviations from this pattern imply either a better patient state, as is the case of solely decreasing doses, or a worse patient state, in the case of increasing doses toward the end of drug administration.

Patient outcome is a reasonable indicator of patient state, especially toward the end of a patient record, but this information will not be available in a real monitoring situation. Ongoing research seeks to obtain a more thorough assessment of patient state based on information that is available in the developing patient record. The successful correlation of patient outcome with certain drug usage patterns indicates that medication administration trends themselves are indicative of patient state. It is also important to realize that in the ICU, intravenous medications are seldom given singly, and combinations of drugs are often indicative of certain pathologies. It may be possible to develop algorithms which can be trained to recognize certain drug usage patterns as indicative of certain disease states. Such algorithms could be used to aid in the annotation of large-scale databases such as MIMIC II. Similar software may also play an integral part in an advanced patient monitoring system which can continuously track the hemodynamic state of a patient as it evolves throughout his or her stay.

5.3 Visualizing the History of a Patient's Response to Medication

The goals of advanced patient monitoring include the ability to assess current patient state, predict the future trajectory of that state, and provide relevant hypotheses to explain abnormal findings. The results of this project have shown that by synthesizing multiple types of information, for example charted medication dose and mean blood pressure trend data, it is possible to obtain a more complete picture of patient state than is available from each trend alone. By combining the information contained in drug dose and blood pressure trends, it is not only possible to rapidly assess the current patient response to a medication, but it becomes easier to track the trajectory of that response and to predict future reactions to medication changes. Future algorithms will no doubt use similar techniques to combine even more types of information into a more detailed picture of patient state.

6 References

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Appendix A: MIMIC II Tables

Several tables in MIMIC II contain information regarding IV medications administered, but they cannot be used to obtain the continuous drug dose as a function of time. These other tables are described in this section. More detailed information regarding the unused fields in the `medevents` table is also included here (Section A.6).

A.1 Additives

The `additives` table contains information on medications which were ordered for a patient, but which may not have been administered. It includes identification numbers which link to both the drug administered (`itemid`) and the particular solution mixed (`ioitemid`). These two numbers should link to labels which make sense together, for example, an `itemid` which corresponds to "Ativan" and an `ioitemid` which corresponds to "D5W 400.0ml + 40mg Ativan" might be seen in the same row of the `additives` table. The `additives` table should contain all of the medications included in the `ioevents` or `medevents` tables, but may contain quite a few more which were not actually administered. The additives table also contains no information about dose or rate of administration. Table A1 lists the fields found in the additives table and a brief description of the information they contain, if known.

Table A1. Descriptions of fields in the `additives` table.

Field name	Description
`pid`	Patient identification number
`charttime`	Date and time that information was charted by caregiver
`chartdate`	Coded date number
`itemid`	Identifies the medication given; links to d_meditems table
`ioitemid`	Identifies the solution given; links to d_ioitems table
`amount`	Amount of drug mixed in solution
`doseunits`	Units of administration
`mlperunit`	Field not populated
`route`	Describes method of administration
`cuid`	Care unit identification number
`cgid`	Caregiver identification number
`scode`	
`pcode`	Field not populated
`sid`	Field not populated
`elemid`	Element identification number
`txid`	Transfer identification number

A.2 Deliveries

It is assumed that the information contained in the `deliveries` table indicates what solutions were delivered for administration to a particular patient. However, the information in this table often does not match that contained in other tables. For example, it does not contain a complete list of those medications which were administered (listed in both the `medevents` and `ioevents` tables), and it often contains drugs which were not administered. It is unknown what the `rate` field refers to in the `deliveries` table, as no units information is contained in the table, and the rate recorded here does not match any of the doses given to the patient

(recorded in medevents) or any of the volumes administered (recorded in ioevents). Table A2 describes what is known about the fields in the deliveries table.

Table A2. Field descriptions for the deliveries table.

Field name	Description
pid	Patient identification number
chartdate	Coded date number.
charttime	Date and time that information was entered by caregiver.
ioitemid	Identifies solution delivered; links to d_ioitems table.
site	Field not populated
rate	Unknown
cgid	Care giver identification number
cuid	Care unit identification number
sid	
elemid	Element identification number
txid	Transfer identification number

A.3 A_iodurations

The a_iodurations table contains each input or output item for a given patient and the length of time over which the patient received that treatment. The items in the a_iodurations table should match those in the ioevents table. The a_iodurations table contains no information about dose or rate of administration. The fields of the a_iodurations table are described briefly in Table A3.

Table A3. Description of fields in the a_iodurations table.

Field name	Description
pid	Patient identification number
itemid	Identifies the solution administered; links to d_ioitems table
starttime	The first recorded time of administration for a particular solution
endtime	The last recorded time of administration for a particular solution
cuid	Care unit identification number
duration	The time, in minutes, between starttime and endtime
scode	Field not populated
pcode	Field not populated
sid	
elemid	

A.4 Ioevents

The ioevents table contains information on the volume of each solution administered over the course of a patient's stay. Basically, it breaks down the total fluid balance into individual items. In addition to solutions of intravenous medications, the ioevents table also contains input items such as "Packed RBC's" (red blood cells) or ".9% Normal Saline" as well as output items such as "Urine Out Foley." Information regarding the volume of intravenous medications delivered can be found here and converted into dose, which should match the doses recorded in the medevents table. For example, if the volume of "D5W 250.0ml + 400mg Dopamine" delivered is 20 mL in the last 30 minutes, and the patient's weight is known to be 100 kg, dose is calculated in the following manner:

(400 mg / 250.0 ml) * (20 ml / 30 min) * 1000 mcg/mg / 100 kg = 10.67 mcg/kg/min

Ideally, the information contained in the ioevents table regarding medications should match that contained in the medevents table. However, even minimal investigation reveals that while they match often, many discrepancies exist. Many of these are the result of missing values in the dose or volume fields in medevents or ioevents. These missing values sometimes correspond to a dose of 0, and sometimes seem to indicate that the previous recorded dose is valid at the current chart time. It was also observed that in many instances, the times where dose changes occur can be off by 15 minutes or more. Both tables also contain a stopped field which indicates when a drug has been discontinued briefly or restarted. These fields do not always match between tables. The prevalence of all these types of discrepancies is unknown. In the ICU, when a nurse records a dose change, she enters information which is very similar to that contained in the medevents table, that is, she records the dose at a given charted time. This information is then processed internally to populate ioevents. It is possible that this internal process produces some of the table discrepancies, and it is assumed that the medevents table is closer to the actual dose administered, but it is impossible to confirm this.

Table A4 describes the fields contained in the ioevents table. Several fields in the table are not populated, and have been excluded from the table. These fields are dressingchanged, tubingchaged, assessment, and pcode.

Table A4. Descriptions of fields in the ioevents table.

Field name	Description
pid	Patient identification number
charttime	Date and time ioevents information was entered by caregiver
realtime	Internal timestamp, date and time ioevents information transferred into database
itemid	Identifies the solution administered to patient; links to d_ioitems table
altid	Alternate identification number, also links to d_ioitems table, but does not generally provide a label which is an "alternate" to the one found using itemid
volume	Volume administered, in mL, between the previous and current charttimes
volumeuom	Volume units of measure, always "ml"
unitshung	When populated, probably indicates the number of bags of solution hung
unitshunguom	Always "units"
newbottle	When populated, a "1" probably means a new bottle of solution has been started
stopped	Indicates when a fluid input has been stopped, temporarily discontinued or restarted
estimate	
annotation	Sparsely populated, provides additional information about treatment administered.
cgid	Caregiver identification number
cuid	Care unit identification number
scode	
chartdate	Coded date number
sid	
elemid	
txid	

A.5 A_meddurations

The a_meddurations table is similar in structure to the a_iodurations table. It lists all medications given to a patient and the total duration of administration for each. The a_meddurations entries should match those in medevents, however, the a_meddurations table contains no information regarding specific doses administered. Table A5 describes each of the fields in a_meddurations briefly.

Table A5. Description of fields in the a_meddurations table.

Field name	Description
pid	Patient identification number
startrealtime	Time and date corresponding to the realtime entry in the medevents table for a given starttime
starttime	Time and date corresponding to the first recorded administration of the medication
itemid	Identifies the medication administered; links to d_meditems table
endtime	Time and date corresponding to the last recorded administration of the medication
cuid	Care unit identification number
duration	Time, in minutes, between starttime and endtime
scode	Field not populated
pcode	Field not populated
sid	
elemid	

A.6 Medevents

The medevents table contains many other fields besides those used to make the plots of continuous dose as a function of time described in Section 2.1. These are described briefly in Table A6.

Table A6. Description of fields in the `medevents` *table.*

Field name	Description
pid	Patient identification number
charttime	Time and date of information entry by caregiver
itemid	Identifies medication administered; links to d_meditems table
elemid	Element identification number
chartdate	Coded date number
realtime	Time and date at which information was transferred into database, internal timestamp
volume	Does not contain meaningful information, always "0.000"
dose	Dose recorded by caregiver at given charttime
doseuom	Dose units of measure
solutionid	Identifies the solvent; links to d_meditems table
solvolume	The amount of solvent used to form solution
route	The method of administration
site	Field not populated
stopped	Indicates whether a drug has been stopped, generally used when a medication is on hold temporarily but will be resumed
annotation	
cgid	Caregiver identification number
cuid	Care unit identification number
pcode	Field not populated
scode	Field not populated
sid	
txid	Transfer identification number

A.7 Solutions

The solutions table contains information on the solvents administered to each patient. Like the additives table, solutions contains both an itemid which links to the d_meditems table and an ioitemid which links to the d_ioitems table. The former uniquely identifies the solvent part of the solution administered while the latter identifies the entire solution administered. The two labels should make sense together, for example, ".9% Normal Saline" and ".9% Normal Saline 100.0ml + 100U Insulin" might be found on the same row. Like the additives table, the solutions table may contain items which were ordered, but not actually administered to the patient. Table A7 further describes the fields in the solutions table.

Table A7. Descriptions of fields in the `solutions` *table.*

Field name	Description
pid	Patient identification number
charttime	Time and date of information entry by caregiver
itemid	Identifies the solvent administered; links to the d_meditems table
ioitemid	Identifies the solution administered; links to the d_ioitems table
volume	The volume of solvent used to make the solution
doseunits	The units of volume used, generally “ml” though occasionally “vl”
route	The method of solution administration
cgid	Caregiver identification number
cuid	Care unit identification number
scode	Field not populated
pcode	Field not populated
chartdate	Coded date number
sid	
elemid	
txid	