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Variability of Target-controlled Infusion Is Less Than the Variability after Bolus Injection

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Background: **Target-controlled infusion (TCI) drug delivery systems deliver intravenous drugs based on pharmacokinetic models. TCI devices administer a bolus, followed by exponentially declining infusions, to rapidly achieve and maintain pseudo–steady state drug concentrations in the plasma or at the site of drug effect. Many studies have documented the prediction accuracy of TCI devices. The authors' goal was to apply linear systems theory to characterize the relation between the variability in concentrations achieved with TCI devices and the variability in concentrations after intravenous bolus injection.**

Methods: **The authors developed a mathematical model of the variability of any arbitrary method of drug delivery, based on the variability with intravenous bolus injection or the variability with an arbitrary infusion regimen. They tested the model in a simulation of 1,000 patients receiving propofol by simple bolus injection, conventional infusion, or a TCI device. The authors then examined an experimental data set for the same behavior.**

Results: **The variability of any arbitrary infusion regimen, including TCI, is bounded by the variability after bolus injection. This is observed in the simulation and experimental data sets as well.**

Conclusion: **TCI devices neither create nor eliminate biologic variability. For any drug described by linear pharmacokinetic models, no infusion regimen, including TCI, can have higher variability than that observed after bolus injection. The median performance of TCI devices should be reasonably close to the prediction of the device. However, the overall spread of the observations is an intrinsic property of the drug, not the TCI delivery system.**

TARGET-CONTROLLED infusion (TCI) drug delivery systems are now available worldwide, except in the United States. This worldwide availability primarily reflects widespread approval of the Diprifusor (trademarked name owned by AstraZeneca, Wilmington, DE) for propofol drug administration. Although the reasons TCI drug delivery systems have not been approved in the United States remain obscure,[1] it is likely that concerns about the accuracy of such devices have had a significant role in delaying approval.[2]

Investigators have documented the accuracy of TCI delivery for many intravenous anesthetic drugs, including fentanyl,[3–6] alfentanil,[7–10] sufentanil,[11,12] remifentanil,[13,14] propofol,[15–24] etomidate,[25] thiopental,[26] midazolam,[27,28] dexmedetomidine,[29] and lidocaine.[30] One striking feature about the accuracy of TCI devices is that it resembles the accuracy observed after simple infusions or bolus drug delivery.

In this investigation, we used linear system theory to explore the relation between the variability in concentration after bolus injection and the variability in concentration during conventional infusions and TCI drug delivery.

Materials and Methods

Mathematical Proof

Standard pharmacokinetic models for intravenous anesthetic drugs typically represent the concentration after bolus injection as a sum of exponential terms:

$$Cp(t) = \text{Dose} \times \sum_{i=1}^{3} C_i e^{-\lambda_i t}, \quad (1)$$

where Dose is the amount of drug injected, C_i are the coefficients of the pharmacokinetic model, and λ_i are the exponents of the pharmacokinetic model. Because these coefficients and exponents describe how the body "disposes" of a unit bolus of drug, we refer to this sum of exponentials as the *unit disposition function* (UDF). Therefore, the UDF in equation 1 is

$$\sum_{i=1}^{3} C_i e^{-\lambda_i t}.$$

The coefficients and exponents can be transformed into other forms, such as volumes and clearances offering a physiologic interpretation of the pharmacokinetics, or micro rate constants for use in differential equations.§ As is common in pharmacokinetics, the coefficients and exponents are constant. Specifically, they do not change with time or dose. This is referred to as *time-invariant* and *dose-invariant* pharmacokinetics.

Equation 1 implies linear pharmacokinetics. If the dose is doubled, the concentration is doubled. If multiple doses are given, equation 1 is calculated for each dose. After displacing the curves in time to reflect the timing of the doses, the concentration in the body is the sum (or superposition) of the contribution of each dose. The assumption of linearity implies nothing more than this.

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§ For example, convert.xls. Available at: http://anesthesia.stanford.edu/pkpd, under Excel Utilities. Accessed October 29, 2004.

Linear pharmacokinetics are sometimes expressed as the convolution of an input function, $I()$, with the disposition function using the convolution integral

$$Cp(t) = \int_0^t I(\tau) \times \sum_{i=1}^{3} C_i e^{-\lambda_i (t-\tau)} d\tau, \quad (2)$$

where $I(\tau)$ is the input, consisting of one or more bolus injections. For an infusion, $I(\tau)$ consists of a very large number of very small boluses. The integral simply adds up the concentrations from each bolus, after shifting the curves to reflect the timing of the doses (accomplished by the τ and $t - \tau$). Because any infusion regimen, including TCI, can be reduced to series of infinitely small boluses, equation 2 is a general description of the relation between drug administration, $I()$, the pharmacokinetic model,

$$\sum_{i=1}^{3} C_i e^{-\lambda_i t},$$

and the resulting concentrations, $Cp()$. We can simplify our mathematical notation by letting * refer to the operation of convolution and referring to

$$\sum_{i=1}^{3} C_i e^{-\lambda_i t},$$

the unit disposition function, as simply $U(t)$:

$$Cp(t) = I(t)^* U(t). \quad (3)$$

Equations 1, 2, and 3 are all statements of linearity, which is a fundamental characteristic of the standard models used to describe intravenous anesthetics. We can analyze the variability that will be expected with any method of drug delivery based only on an assumption of linearity. First, we define the expected value, E, the SD, σ, and the coefficient of variation (CV) in a conventional way. For any vector $X = (x_1, \ldots, x_n)$ of length n,

$$E(X) = \sum_{i}^{n} \frac{x_i}{n}, \quad (4)$$

$$\sigma(X) = \left\{ \frac{\sum_{i}^{n} (x_i - E(X))^2}{\mathrm{n}} \right\}^{1/2}, \quad (5)$$

$$CV(X) = \frac{\sigma(X)}{E(X)}. \quad (6)$$

Equation 4 states that the expected value of X is the average X. Equation 5 states that the SD is the average squared difference between the average X and each individual observation. Equation 6 states that the CV is the SD divided by the average. Therefore, equations 4, 5, and 6 are standard statistical definitions, but they are introduced here to help clarify the formal proof that follows.

Theorem 1

We now consider the pharmacokinetic variability in a population of patients. Let $U(t) = \{u_i(t)\}$, $i = 1, \ldots, n$ be a collection of unit disposition functions in a population of n patients. We define $\rho_u(t)$ as the CV of the set of UDFs at time t. We also define $M = \max_t \rho_u(t)$, *i.e.*, the maximum value of the CV of the UDFs over time.

Let D_j be a series of consecutive boluses of amount d_j given at time t_j, $j = 1, \ldots k$. Consistent with equations 2 and 3, we define $I(t)$ as the dosing function, which consists of boluses D_j. Let each individual patient receive the same $I(t)$.

We propose that for any arbitrary dosing regimen, $I(t)$, the observed CV in concentration in the population of patients will be less than or equal to M, the maximum CV after unit bolus injection. Stated formally, we propose that for any $I(t)$,

$$\text{For } t \le t_k, \ \ CV(\{U(t)^* I(t)\}) \le M. \quad (7)$$

The proof is as follows:

Let

$$R_{ji}(t) = D_j \cdot u_i(t - t_j) \quad (8)$$

be the response resulting from the jth bolus in the ith individual. Let m be the number of boluses up to time t. The response at time t in the ith individual is the sum of the responses to all preceding boluses,

$$R_i(t) = \sum_{j=1}^{m} R_{ji}(t). \quad (9)$$

It thus follows that the CV of responses at time t is

$$CV(\{U(t)^* I(t)\}) = CV(\{R(t)\}) = CV(\{R_i(t)\}), \quad (10)$$

where

$$\{R_i(t)\} = \left\{ \sum_{j=1}^{m} R_{ji}(t) \right\}, \ i = 1, \ldots, n$$

is the set of responses. Equation 10 can be restated as

$$CV(\{U(t)^* I(t)\}) = \frac{\sigma\left(\left\{ \sum_{j=1}^{m} R_{ji}(t) \right\} \right)}{\mathrm{E}\left(\left\{ \sum_{j=1}^{m} R_{ji}(t) \right\} \right)}. \quad (11)$$

The lemma in the appendix shows that

$$\sigma\left(\left\{ \sum x \right\} \right) \le \sum \sigma(\{x\}). \quad (12)$$

Applying equation 12 to the numerator of the term on the right-hand side, we get

$$CV(\{U(t)^*I(t)\}) = \frac{\sigma\left(\left\{\sum_{j=1}^{m} R_{ji}(t)\right\}\right)}{\mathrm{E}\left(\left\{\sum_{j=1}^{m} R_{ji}(t)\right\}\right)} \leq \frac{\sum_{j=1}^{m} \sigma(\{R_{ji}(t)\})}{E\left(\left\{\sum_{j=1}^{m} R_{ji}(t)\right\}\right)}. \quad (13)$$

Consider only the jth bolus. By definition of M, the maximum CV after the jth bolus injection is

$$\frac{\sigma(\{R_{ji}(t)\})}{E(\{R_{ji}(\mathrm{t})\})} \equiv CV(\{R_{ji}(t)\}) = \rho_u(t-t_j) \leq M, \quad (14)$$

which can be rearranged as

$$\sigma(\{R_{ji}(t)\}) \leq E(\{R_{ji}(t)\})M. \quad (15)$$

Substituting equation 15 in for the upper right numerator in equation 13 yields

$$CV(\{U(t)^*I(t)\}) \leq \frac{\sum_{j=1}^{m} E(\{R_{ji}(t)\})M}{E\left(\left\{\sum_{j=1}^{m} R_{ji}(t)\right\}\right)}, \quad (16)$$

which can be simplified to

$$CV(\{U(t)^*I(t)\}) \leq M. \quad (17)$$

Equation 17 completes the proof for any arbitrary series of boluses. Because an infusion at the limit can be represented by an infinite sum of infinitesimal boluses, the proof also applies to any infusion regimen including conventional infusions and TCI administration.

Simulations

Based on the pharmacokinetics of propofol as reported by Schnider *et al.*,[31] we calculated the expected volumes and clearances for a 50-yr-old man with a weight of 70 kg and a height of 170 cm: $V_1 = 4.27$ l, $V_2 = 20.07$ l, $V_3 = 238$ l, $Cl_1 = 1.64$ l/min, $Cl_2 = 1.36$ l/min, $Cl_3 = 0.84$ l/min. We then created a population of 1,000 individuals whose volumes and clearances varied by 30% (log-normally distributed) from the nominal individual.

This population of individuals was given a 10-mg bolus of propofol (simulation 1), a propofol infusion of 10 mg/min (simulation 2), or TCI administration of propofol intended to achieve a target concentration of 1.0 μg/ml in the nominal individual (simulation 3). The variability in concentration between the bolus results and the infusion regimens were compared.

The simulation was performed in Excel (Microsoft Corporation, Redmond WA). The CV at each point in time was calculated in the standard manner (equation 6).

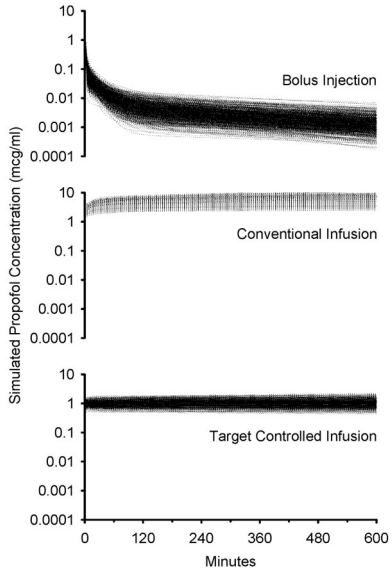

Fig. 1. Simulation of 1,000 patients receiving either a 10-mg bolus of propofol (*top graph*), a propofol infusion at 10 mg/min (*middle graph*), or a target-controlled infusion of propofol at a target plasma concentration of 1 μg/ml (*bottom graph*). The log scale permits visual assessment of the coefficient of variation for the three drug delivery paradigms. The coefficient of variation is greater with bolus injection.

Experimental Data

Although our laboratory has been associated with many studies involving target-controlled drug administration, most of these have used pharmacokinetics derived from brief infusions. The only TCI study based on bolus pharmacokinetics for which we still have the original data from both bolus and TCI regimens was a study in rats receiving thiopental.[32] We used these data to examine whether the predictions of the mathematical proof and the simulations were observed in experimental data. The CV was calculated using Excel.

Results

Mathematical Proof

The proposition that the variability with any infusion regimen, including TCI, cannot exceed the variability observed with bolus injection over the same time period has been shown to be a fundamental property of any drug described by linear pharmacokinetic models. This applies to all intravenous anesthetic drugs.

Simulations

Figure 1 shows the simulations based on 1,000 individuals receiving a 10-mg bolus of propofol (top graph), a propofol infusion of 10 mg/min (middle graph), or TCI administration targeting a propofol concentration of 1 μg/ml (bottom graph). The individual trajectories are represented as dotted lines, permitting visual assessment of the overall range in concentrations for the three methods of drug delivery. The simulations are plotted on

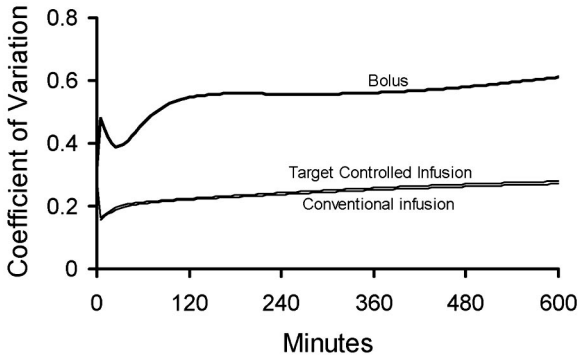

Fig. 2. Coefficients of variation for the simulations of 1,000 patients for the bolus injection, the conventional infusion, and the target-controlled infusion. These are the same patients whose individual concentrations over time are shown in figure 1. The coefficients of variation for conventional infusions and target-controlled infusions are indistinguishable and are well below the coefficient of variation after bolus injection.

identical log scales, permitting direct visual comparison of the relative spread of the data independent of the scale of the data.

In these simulations, the variability with bolus injection was approximately twice the variability observed with a conventional infusion or TCI administration. Figure 2 shows the CV over time after the bolus injection, the conventional infusion, and TCI administration. The coefficients of variation with the conventional infusion and TCI administration are indistinguishable and are approximately half that after bolus injection.

Experimental Data

The top graph in figure 3 shows the concentrations observed in nine rats after identical bolus injections of thiopental. The average CV over the measured time points was 31%. The pharmacokinetics from these first nine rats were then programmed into a TCI device, which was used to deliver thiopental to seven additional rats, who received two different target regimens (fig. 3, middle graphs, left and right). The CV from this first TCI infusion was 11%. A persistent overshoot of the target-controlled concentration occurred in these seven rats, so their data were used to derive a second thiopental pharmacokinetic data set. When this second set was prospectively tested in eight additional rats (fig. 3, bottom graphs, left and right), the overshoot was eliminated. The CV in the second TCI infusion was 18%. In this study, the variability seen after bolus injection (fig. 3, top graph) is greater than the variability observed in the four different TCI regimens (fig. 3, middle and bottom graphs).

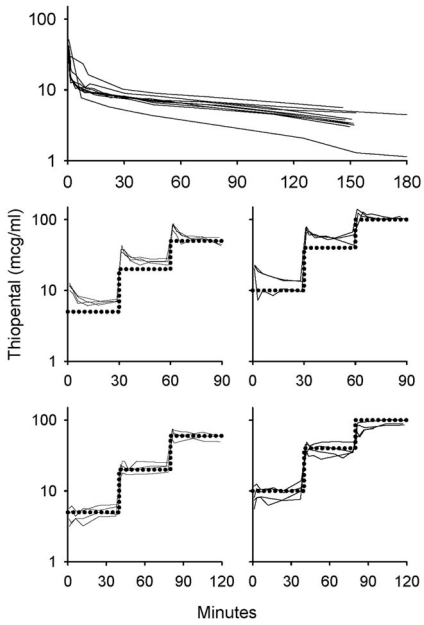

Fig. 3. Results of a previous study in rats in which thiopental was given as bolus injection (*top graph*; coefficient of variation = 31%) or as target-controlled infusions (TCIs) (*four lower graphs*). The *middle two graphs* are a prospective result (coefficient of variation = 11%) obtained with the TCI programmed using the pharmacokinetics derived from the bolus injection study (*top graph*). The lower two graphs are a prospective result (coefficient of variation = 18%) obtained with the TCI programmed using the pharmacokinetics derived from the first TCI study (*i.e.*, a refinement of the first TCI model, based on pharmacokinetic analysis of the *middle two graphs*). The *dotted line* shows the target concentrations for the TCI administrations. The variability observed with target-controlled drug delivery is less than that after bolus injection, as predicted by the formal mathematical analysis and the simulations.

Discussion

Target-controlled infusion devices offer the convenience of allowing clinicians to specify a target drug concentration rather than a particular infusion rate. The theoretical benefits of giving anesthesia by specifying a target concentration rather than an infusion rate were explored in a recent editorial in ANESTHESIOLOGY.[1] TCI devices have been associated with biologic variability, reflecting the desire of investigators to obtain an accurate prediction of concentration. Although this effort to obtain an accurate prediction is commendable, the accuracy of the prediction is inexorably limited by biologic variability. The transformation of a drug administration profile to a plasma or effect site concentration is done by each individual patient's body. TCI devices are not responsible for biologic variability. The case has been made that biologic variability prevents safe use of TCI devices.[2] This is nonsense.

There are two mechanisms by which TCI devices decrease, rather than increase, biologic variability. The first is that TCI devices can incorporate patient covariates such as weight, height, age, sex, liver function, or cardiac output into the pharmacokinetic model. In the future, pharmacogenetic covariates may also be incorporated into pharmacokinetic models. The patient-specific model is then used to control the drug administration, providing an infusion tailored to the pharmacokinetics

Table 1. Simple Example Showing How Two Boluses Will Produce Less Variability in Response Than a Single Bolus

	Bolus 1			Bolus 2			Bolus 1 + Bolus 2		
Time	Mean	CV	SD	Mean	CV	SD	Mean	SD	CV
0	4.00	0	0				4.00	0	0
10	2.00	0	0	4.00	0	0	6.00	0	0
20	1.00	0.5	0.5	2.00	0	0	3.00	0.5	0.17
30	0.50	0	0	1.00	0.5	0.5	1.50	0.5	0.33
40	0.25	0	0	0.50	0	0	0.75	0	0

The two identical boluses, given 10 min apart (third column group), yields a time course with a smaller maximum coefficient of variation (CV) than a single bolus given at time 0 (first column group).

of the patient. Complex patient covariates (*e.g.*, age-related reduction in intercompartmental compartmental clearance) are virtually impossible to incorporate into drug dosing without TCI. As the science of drug pharmacokinetics produces ever more complex models, including physiologically based models and models incorporating complex genetic traits, there will be increasing need for TCI devices to translate these advances into accurate drug administration.

The second mechanism by which TCI devices decrease variability is by understanding the pharmacokinetic influence of drug accumulation in peripheral tissues. As a result of understanding accumulation, setting a particular target concentration on a TCI device typically results in achieving a steady concentration in the patient. By contrast, setting a particular rate on an infusion pump results in increasing drug concentrations over time as drug accumulates in peripheral tissues. Therefore, TCI devices achieve a more predictable relation between the device setting and drug effect than is possible with conventional infusions.[1]

Based simply on linear systems theory, with the only assumptions being linearity with respect to dose and time invariance, the coefficient in variation in concentration after any input cannot exceed the coefficient in variation in concentration after bolus injection. Put in another way, no infusion system can add variability over that observed after bolus injection. In addition, the greatest coefficient in variation with any infusion system within a given time period is bounded above by the variability after bolus injection within the same time period. For example, if one is concerned about the variability in the first 10 min of a TCI device, this variability bounded by the maximum variability within the first 10 min after bolus injection.

A simple intuitive explanation may help to explain the mathematical proof. Let us assume that after a fixed bolus injection of Duzitol, a fictitious drug,[33] patients have identical concentrations at all times except at 20 min. At 0, 10, 20, 30, and 40 min, the concentrations are $4 \pm 0\%$, $2 \pm 0\%$, $1 \pm 50\%$, $0.5 \pm 0\%$, and $0.25 \pm 0\%$ CV, respectively, as shown in table 1. Now, consider giving two identical boluses of Duzitol to the same population of patients, the first given at time 0 and the next given 10 min later. The resulting concentrations are shown in the right columns in table 1. Because the times of maximum CV for the two boluses do not line up, the maximum CV after two boluses (table 1, far right column) is less than the maximum after a single bolus.

There are many drugs whose variability when given by bolus injection is low enough that they are routinely given by bolus injection. Common examples in anesthesia include fentanyl, alfentanil, sufentanil, remifentanil, morphine, hydromorphone, propofol, etomidate, thiopental, ketamine, pancuronium, vecuronium, atracurium, cisatracurium, dexmedetomidine, midazolam, and lorazepam. Because the variability in resulting concentrations for TCI does not exceed the variability in resulting concentrations for bolus injection, it follows that TCI administration of these drugs should also yield concentrations with acceptably low variability to be clinically useful.

Of course, this analysis is about the unexplained intersubject pharmacokinetic variability. Both the mathematical proof and the simulations ignored assay error. Assay error would be the same regardless of the method of drug delivery. Model misspecification does not influence the proof because the proof does not depend on any specific model other than linearity.

This analysis also ignores the accuracy of the pump mechanism, and the faithful reproduction of the pharmacokinetic model by the TCI device. It is possible that the frequent requests for rate changes could affect pump accuracy with a TCI device more than with a conventional infusion device. TCI pumps meet the same standards of pumping accuracy as any other infusion device. Computer-controlled pumps have been evaluated for accuracy, with acceptable results.[34,35] Similarly, the pharmacokinetic software in TCI devices should meet appropriate standards for software development and validation. The software for the Diprifusor has been rigorously tested by regulatory agencies.[36,37] Parenthetically, all contemporary infusion systems are controlled by computer software, and the software required to execute the pharmacokinetic model is trivial compared with the software required for the user interface, stepper motor tracking, pump error handling, and other essential functions of infusion devices.

Conventional infusion pumps make no claim that they will reach any concentration, so the user holds them to a standard of delivering a set volume over time. The TCI user may expect the pump to achieve the predicted concentration with similar accuracy to the mechanical accuracy of a conventional infusion pump. This expectation confuses mechanical variability, present in both devices, with biologic variability, over which the TCI device has little control. In addition, this is not the correct way to interpret the target concentration. The target concentration defines, within the pumping accuracy of the device, an exact dosing regimen. The target is, in fact, the dose. Many manuscripts now report TCI target concentration–*versus*–response relations. These are simply dose–response relations, but they take advantage of the ability of TCI devices to achieve a pseudo–steady state. In addition, the exact dose (amount of drug over time) specified by the target concentration can be readily calculated. As such, the infusion rates called for at a given target concentration can be compared with the range of doses specified in the drug labeling to demonstrate whether they conform to the package insert.

Target-controlled infusion devices give approved drugs for approved indications by approved routes at doses that can be shown to conform to the label of the drugs being administered. They do not contribute to biologic variability. They can reduce biologic variability by incorporating patient specific covariates into advanced pharmacokinetic models to individual drug dosing.

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Appendix: Lemma 1

Consider two sets of identical length, $\{x_1\}$ and $\{x_2\}$. Because the square of any number is zero or positive, it follows that

$$0 \le \left[\sigma(\{x_1\}) - \frac{\text{covariance}(\{x_1\}, \{x_2\})}{\text{var}(\{x_2\})}\sigma(\{x_2\}) \right]^2. \quad \text{(A1)}$$

Equation A1 can be expanded to

$$0 \le \text{var}(\{x_1\}) - 2\frac{\text{covariance}(\{x_1\}, \{x_2\})}{\text{var}(\{x_2\})}\sigma(\{x_1\})\sigma(\{x_2\}) + \frac{\text{covariance}(\{x_1\}, \{x_2\})^2}{\text{var}(\{x_2\})^2}\text{var}(\{x_2\}). \quad \text{(A2)}$$

Equation A2 can be algebraically simplified to

$$0 \le \text{var}(\{x_1\}) - \frac{\text{covariance}(\{x_1\}, \{x_2\})^2}{\text{var}(\{x_2\})}. \quad \text{(A3)}$$

Equation A3 can be rearranged as

$$\text{covariance}(\{x_1\}, \{x_2\})^2 \le \text{var}(\{x_1\})\text{var}(\{x_2\}). \quad \text{(A4)}$$

Taking the square root of both sides of equation A4 yields

$$\text{covariance}(\{x_1\}, \{x_2\}) \le \sigma(\{x_1\})\sigma(\{x_2\}). \quad \text{(A5)}$$

If we multiply each side of equation A5 by 2 and add variance(x) + variance(y) to each side, we get

$$2 \cdot \text{covariance}(\{x_1\}, \{x_2\}) + \text{var}(\{x_1\}) + \text{var}(\{x_2\}) \le 2 \cdot \sigma(\{x_1\})\sigma(\{x_2\}) + \text{var}(\{x_1\}) + \text{var}(\{x_2\}). \quad \text{(A6)}$$

Taking the square root of each side of equation A6 gives

$$\sigma(\{x_1 + x_2\}) \le \sigma(\{x_1\}) + \sigma(\{x_2\}). \quad \text{(A7)}$$

Because the set of numbers x_2 could represent the sum of other sets, $x_2 + x_3$, it follows that

$$\sigma(\{x_1 + x_2 + x_3\}) \le \sigma(\{x_1\}) + \sigma(\{x_2\}) + \sigma(\{x_3\}), \quad \text{(A8)}$$

or, more generally,

$$\sigma\left(\left\{\sum x\right\}\right) \le \sum \sigma(\{x\}). \quad \text{(A9)}$$