

# Estimation of the Optimal Statistical Quality Control Sampling Time Intervals Using a Residual Risk Measure

# Aristides T. Hatjimihail\*

Hellenic Complex Systems Laboratory, Drama, Greece

# **Abstract**

**Background:** An open problem in clinical chemistry is the estimation of the optimal sampling time intervals for the application of statistical quality control (QC) procedures that are based on the measurement of control materials. This is a probabilistic risk assessment problem that requires reliability analysis of the analytical system, and the estimation of the risk caused by the measurement error.

Methodology/Principal Findings: Assuming that the states of the analytical system are the reliability state, the maintenance state, the critical-failure modes and their combinations, we can define risk functions based on the mean time of the states, their measurement error and the medically acceptable measurement error. Consequently, a residual risk measure rr can be defined for each sampling time interval. The rr depends on the state probability vectors of the analytical system, the state transition probability matrices before and after each application of the QC procedure and the state mean time matrices. As optimal sampling time intervals can be defined those minimizing a QC related cost measure while the rr is acceptable. I developed an algorithm that estimates the rr for any QC sampling time interval of a QC procedure applied to analytical systems with an arbitrary number of critical-failure modes, assuming any failure time and measurement error probability density function for each mode. Furthermore, given the acceptable rr, it can estimate the optimal QC sampling time intervals.

Conclusions/Significance: It is possible to rationally estimate the optimal QC sampling time intervals of an analytical system to sustain an acceptable residual risk with the minimum QC related cost. For the optimization the reliability analysis of the analytical system and the risk analysis of the measurement error are needed.

Citation: Hatjimihail AT (2009) Estimation of the Optimal Statistical Quality Control Sampling Time Intervals Using a Residual Risk Measure. PLoS ONE 4(6): e5770. doi:10.1371/journal.pone.0005770

Editor: Fabio Rapallo, University of East Piedmont, Italy

Received February 11, 2009; Accepted May 4, 2009; Published June 9, 2009

**Copyright:** © 2009 Hatjimihail. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1

Funding: The author has no support or funding to report.

Competing Interests: The author has declared that no competing interests exist.

\* E-mail: ath@hcsl.com

### Introduction

In clinical chemistry the minimal required frequency of statistical QC applied to analytical systems has been the testing of at least one control sample per level of concentration of the measurand, at two levels of concentration, once per 24 hr. A few years ago the Clinical Laboratory Improvement Amendments (CLIA) recommendation of the "equivalent QC" was issued [1]. According to that recommendation the control materials based QC that is not built in the test system but is applied by the user is characterized as "external" QC, while the "internal monitoring systems that are a part of or built into the test system are called electronic, internal, or procedural controls". The required "external" QC frequency can be reduced to once per month or once per week, after an initial evaluation period of successful daily QC testing. A system to be eligible for the QC frequency of once per month should include an internal monitoring system. The "equivalent QC" concept has implicitly introduced the reliability concept of the critical-failure rate into QC planning. The system is evaluated by daily QC testing for a certain period of time. If the evaluation is successful then it is assumed a critical hazard rate less than an implicit threshold and a less frequent QC is required. On the other hand less frequent QC is required if the system includes an internal monitoring system, as this system detects the potential critical failures, except if it fails too. In that case the hazard rate of the system is the rate of a combined potential critical failure of the analytical subsystem and of the internal monitoring system. The equivalent QC concept has initiated a debate about the optimal QC frequency.

There have been proposed optimization methods of the QC procedures applied to clinical chemistry analytical systems [2–4]. They maximize the probability of rejection, assuming that certain significant measurement error has been introduced into the measurements, while keeping the probability for false rejection less than a certain threshold. There also have been references to the run length. In their paper, Westgard, Koch and Oryall [5] used the batch size and the observed frequency of errors to estimate the test yield and defect rate. To estimate the test yield they proposed an expanded productivity model that included an estimation of the repetition of the tests because of the erroneous results. Parvin and Gronowski proposed performance measures based on the analytical run length and the number of patient samples with unacceptable error [6]. Parvin and Robbins estimated the mean time "from the occurrence of an out-ofcontrol error condition to the next scheduled QC event", assuming an exponential distribution of failure, to compare the performance of randomized versus fixed-time schedules of QC procedures [7]. Recently, Parvin used a worst case of measurement error scenario estimation of the number of the samples nonconforming the quality specifications to propose a definition of the sampling time interval [8]. Nevertheless, in clinical chemistry the estimation of the optimal sampling time intervals for the application of statistical quality control (QC) procedures that are based on the measurement of control materials remains an open problem.

In the QC literature there have been papers on the economic design of the  $\overline{x}$ -control charts, optimizing the number of the controls, the decision limits and the sampling time interval to minimize the cost. Duncan proposed a fixed run length optimization method, assuming one failure mode with an exponential distribution of failures [9], while Banerjee and Rahim proposed an elegant variable run length optimization method, assuming one failure mode with a Weibull distribution of failures [10]. In addition they optimized the number of the controls and the decision limits to minimize the cost of the production process, including the QC cost. Linderman, McKone-Sweet, and Anderson [11], and recently Panagiotidou and Nenes [12] have proposed an integrated approach to process control and maintenance.

The explosive growth of the complexity of the clinical laboratories and of their analytical systems increases exponentially the difficulty of their management. New quantitative tools are needed to assist the sound judgment of their directors so that they can take optimal or near optimal decisions. We are actually experiencing a paradigm shift in the management of the clinical laboratories, as new techniques are introduced from other fields. Particularly promising are the risk management techniques that have recently been applied in some clinical laboratories, although they have already been extensively and successfully used in engineering.

As risk management is defined "the systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk" [13]. Risk is "the combination of the probability of occurrence of harm and the severity of that harm" while *hazard* is "the potential source of harm". Residual risk is the risk remaining after the control measures have been taken. To be applied to the analytical systems risk management needs to be supplemented by reliability analysis. Reliability is "the probability that an item will perform a required function, under stated conditions, for a stated period of time". Reliability is therefore the extension of quality into the time domain and may be paraphrased as "the probability of non-failure in a given period" [14]. Failure is the "termination of the ability of an item to perform a required function", while critical failure is "a failure that can initiate hazard".

Actually, the QC planning problem of the analytical process can be translated into a probabilistic risk assessment problem. The reliability analysis of an analytical system should include a quantitative fault tree analysis [15] to define the critical-failure modes and estimate the critical-failure time and measurement error probability density functions and their dependencies. A critical failure of an analytical system in a clinical laboratory setting can initiate hazard when the total measurement error of a result of a patient exceeds the medically acceptable measurement error. This incorrect result can cause harmful medical decisions. The risk of a critical failure is associated with the probability that it will occur and with the time that it will persist. The applied QC procedure detects a critical failure with a certain probability. As residual risk can be considered the risk of the measurement process, assuming the application of the QC procedure. We can define risk measures based on the partial moments of the measurement error with reference to the medically acceptable measurement error (see Partial moments in Appendix S1). Then we can estimate the risk before the application of the QC and the residual risk assuming QC is applied.

There is a certain financial cost associated with the QC, including the cost of the control materials and their measurements and the cost of the repetitions because of the rejections. Therefore, an operational approach to the optimal QC sampling planning could be based on the minimization of the QC related cost while the residual risk is acceptable.

To explore the estimation of the QC sampling time intervals using a residual risk measure I developed an algorithm that estimates the residual risk of any sampling time interval of QC procedures applied to analytical systems with an arbitrary number of critical-failure modes, assuming any probability density function of critical-failure time and measurement error for each mode. Furthermore it can estimate the optimal OC sampling time intervals that minimize a OC related cost measure.

#### Methods

The Mathematica® 7.0 mathematical program was used for the development of the algorithm. A personal computer with an Intel Quad Core<sup>®</sup> 2.8 GHertz CPU, 8 GBytes of RAM, and the 64-bit Windows Vista® operating system was used for the estimation of the data.

Using advanced numerical methods the algorithm I developed estimates the residual risk of any sampling time interval of a QC procedure applied to analytical systems with an arbitrary number of critical-failure modes, assuming any probability density function of critical-failure time and measurement error for each mode. Furthermore it can estimate the optimal QC sampling time intervals  $[t_{i-1},t_i]$  to minimize a QC related cost measure, given the maximum acceptable residual risk measure rr.

## The model

The algorithm is based on a model that simulates a clinical analytical system. The main components and parameters of the model are:

- 1. The medically acceptable measurement error.
- 2. The states *S* of the model:
  - The *n* critical-failure modes  $F_h$  and their combinations. The critical-failure modes can be independent or dependent upon each other.
  - The reliability state R.
  - The maintenance state M.
- 3. The critical-failure time probability density functions  $f_h$  of each critical-failure mode  $F_h$ .
- 4. The measurement error probability density functions:
  - The measurement error probability density function g<sub>0</sub> of the reliability state R.
  - The measurement error probability density function  $g_h$  of each critical-failure mode  $F_h$ .
- 5. The initial time  $t_0$  and the initial state probability vector  $\mathbf{p}_0(\mathbf{s}_n)$ of the system (see eqs (41) and (42)).
- 6. The series of the measurements performed at each QC sampling time interval  $(t_{i-1},t_i)$ .
- 7. The applied QC procedure:

- The c levels of the concentration of the measurand of the
- The number of the controls at each level b.
- The OC rules
- 8. The risk functions of the states.
- 9. The QC related cost functions of the states.

#### **Definitions**

The definitions of the functions, vectors, matrices and equations (see Notation in Appendix S1) used for the simulations are given with the following additional assumptions:

- 1. For  $t_0 = 0$  the initial state of the system is the reliability state R.
- 2. The algorithm is applied until the system enters the maintenance state.
- 3. There are one or two critical-failure modes  $F_h$ .
- 4. The critical-failure time probability density functions  $f_h$  of each critical-failure mode are general distributions.
- 5. The critical-failure modes and their time probability density functions  $f_h$  are independent.
- 6. The probability density function  $g_0$  of the reliability state is the unit normal distribution. Therefore,  $\mu_0 = 0$  and  $\sigma_0 = 1$ , where  $\mu_0$  and  $\sigma_0$  are the mean and the standard deviation of the  $g_0$ . The probability density function  $g_h$  of the measurement error of each critical-failure mode is either the normal distribution or a mixture distribution that models the intermittent measurement error. If the system fails with two combined failure modes, then an additive measurement error model is assumed.
- 7. The probability density functions of the measurement error at each level of the controls are the same. If the probability density functions of the measurement error of the c levels of the concentration of the measurand of the controls are different, then multivariate probability density functions can be used (See Definition of functions assuming multivariate measurement error probability density functions in Appendix S1).
- 8. The OC rules are single value rules with decision limit l [16], applied at the end of the QC sampling time interval upon one control per level at c levels of controls.
- 9. The rejection of an analytical run by the QC procedure causes the transition of the analytical system to the maintenance state.
- The measurement error, the critical measurement error, the medically acceptable measurement error, and the decision levels l of the controls are measured in  $\sigma_0$  units, where  $\sigma_0$  is the standard deviation of the measurement error of the reliability state.
- 11. The time is measured in arbitrary time units.
- The cost is measured in cost per unit of time of operation in the reliability state units.
- The risk of the states is a function of the  $d^{th}$  partial moments of their measurement error with reference to the medically acceptable measurement error.
- The OC related cost of the states for a sampling time interval is the cost cq of the c controls, where q is the cost of each control sample and its mesurement. In addition, the OC related cost of the maintenance state includes a cost m and the cost of the repetitions of the analysis of the controls and the samples.

# Definition of the functions

**Reliability functions.** The analytical systems fail with a certain probability during their lifetime. Usually there are several failure modes. Assuming that  $f_i(t)$  is the failure time probability density function of the  $j^{th}$  failure mode, the respective mean time to failure is defined as

$$MTF(F_j) = \int_{0}^{\infty} f_j(t)tdt$$
 (1)

while the hazard rate is defined as

$$HR(F_j) = \frac{f_j(t)}{1 - \int_0^t f_j(z)dz}$$
 (2)

We may assume that

$$f_i(t) =$$

$$\left( \gamma_j \lambda_j \alpha_j t^{\alpha_j - 1} + (1 - \gamma_j) \beta_j t^{\beta_j - 1} \theta_j e^{\theta_j t^{\beta_j}} \right) e^{-\gamma_j \lambda_j t^{\alpha_j} - (1 - \gamma_j) \left( e^{\theta_j t^{\beta_j}} - 1 \right)}$$
 (3)

where  $\alpha_i$ ,  $\beta_i$ ,  $\theta_i$ , and  $\lambda_i \ge 0$  and  $0 \le \gamma_i \le 1$ . This distribution is called general distribution [17].

For  $\alpha_i = 1$  and  $\gamma_i = 1$ , we have the exponential distribution:

$$f_i(t) = \lambda_i e^{-\lambda_i t} \tag{4}$$

while i.e, for  $\alpha_i = 0.5$  and  $\beta_i = 1$  we have a distribution with a bathtub hazard rate curve (figure 1).

The probability that the system fails at the i<sup>th</sup> time interval because of the  $j^{th}$  mode is:

$$P_i(F_j) = \int_{t_{i-1}}^{t_i} f_j(t)dt$$
 (5)

The conditional probability that the system fails at the  $i^{th}$  time interval because of the j<sup>th</sup> mode, given that it has not failed because of this failure mode at the time  $t_{i-1}$  is:

$$Pc_{i}(F_{j}) = \frac{\int_{t_{i-1}}^{t_{i}} f_{j}(t)dt}{1 - \int_{0}^{t_{i-1}} f_{j}(t)dt}$$
(6)

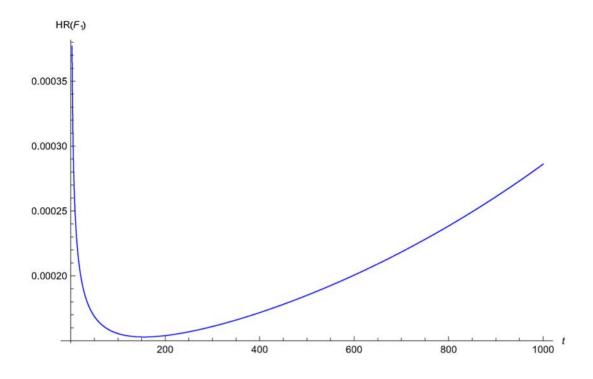
The probability that the system fails at the  $i^{th}$  sampling time interval because of the  $j^{th}$  and  $h^{th}$  failure modes is:

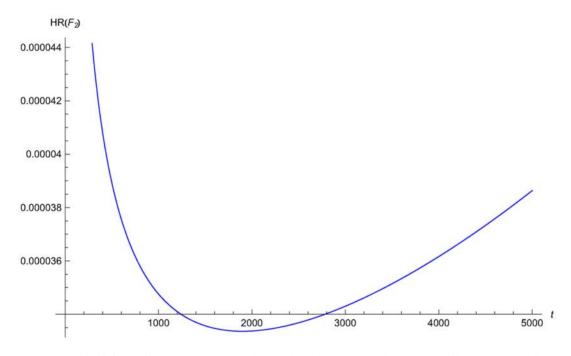
$$\mathbf{P}_{i}(F_{h}, F_{j}) = \int_{t_{i-1}}^{t_{i}} \mathbf{f}_{h,j}(t)dt \tag{7}$$

Assuming that the two failure modes are independent, we have:

$$\mathbf{f}_{h,j}(t) = \mathbf{f}_h(t)\mathbf{f}_j(t) \tag{8}$$

Therefore, the conditional probability that the system fails at the same sampling time interval because of the  $j^{th}$  and  $h^{th}$  failure modes, given that it has not failed because of these failure modes at





**Figure 1. Bathtub hazard rate curves.** Upper plot: The hazard rate  $HR(F_1)$  of the general failure time probability density function for  $\alpha_1 = 0.5$ ,  $\beta_1 = 1$ ,  $\gamma_1 = 0.9$ ,  $\theta_1 = 0.001$ , and  $\lambda_1 = 0.001$ , with a bathtub curve. Lower plot: The hazard rate  $HR(F_2)$  of the general failure time probability density function for  $\alpha_2 = 0.5$ ,  $\beta_2 = 1$ ,  $\gamma_2 = 0.8$ ,  $\theta_2 = 0.0001$ , and  $\lambda_2 = 0.001$ , with a bathtub curve. doi:10.1371/journal.pone.0005770.g001

the time  $t_{i-1}$  is:

$$Pc_{i}(F_{h}, F_{j}) = \frac{\int_{t_{i-1}}^{t_{i}} f_{h,j}(t)dt}{1 - \int_{0}^{t_{i-1}} f_{h,j}(t)dt} = \frac{\int_{t_{i-1}}^{t_{i}} f_{h}(t)f_{j}(t)dt}{1 - \int_{0}^{t_{i-1}} f_{h}(t)f_{j}(t)dt}$$
(9)

The conditional probability that the system fails at the  $i^{\rm th}$ sampling time interval because of the  $h^{th}$  failure mode, given that it has failed because of the  $i^{th}$  failure mode before the  $i^{th}$  sampling time interval, is:

$$P_i(F_h, F_j | F_j) = \int_{t_{i-1}}^{t_i} f_{h,j|j}(t)dt$$
 (10)

Assuming that the failure time probability density functions of the two failure modes are independent, we have:

$$f_{h, j|j}(t) = \frac{f_h(t)f_j(t)}{f_j(t)} = f_h(t)$$
 (11)

Therefore:

$$\mathbf{P}_i(F_h, F_i|F_i) = \mathbf{P}_i(F_h) \tag{12}$$

and

$$Pc_i(F_h, F_i|F_i) = Pc_i(F_h)$$
(13)

If the failure time probability density functions of the two failure modes are dependent, we have

$$f_{h,i}(t) = \text{Co}_{h,i}(f_h(t), f_i(t))$$
 (14)

and

$$f_{h,j|j}(t) = \frac{\text{Co}_{h,j}(f_h(t), f_j(t))}{f_j(t)}$$
(15)

where  $Co_h(f_h(t), f_h(t))$  is a bivariate dependence function.

The expected time from the failure of a system because of the  $i^{th}$ failure mode until the time  $t_i$ , given that the failure has happened at the  $i^{th}$  sampling time interval is:

$$MT_{i}(F_{j}) = t_{i} - \frac{\int_{t_{i-1}}^{t_{i}} f_{j}(t)(t - t_{i-1})dt}{\int_{t_{i-1}}^{t_{i}} f_{j}(t)dt}$$
(16)

The expected time from the failure of a system because of the j<sup>th</sup> and  $h^{\text{th}}$  failure modes until the time  $t_i$ , given that the failure has happened at the  $i^{th}$  sampling time interval, and that the two modes are independent is:

$$MT_{i}(F_{j}, F_{h}) = t_{i} - \frac{\int_{t_{i-1}}^{t_{i}} f_{h, j}(t)(t - t_{i-1})dt}{\int_{t_{i-1}}^{t_{i}} f_{h, j}(t)dt}$$

$$= t_{i} - \frac{\int_{t_{i-1}}^{t_{i}} f_{j}(t)f_{h}(t)(t - t_{i-1})dt}{\int_{t_{i-1}}^{t_{i}} f_{j}(t)f_{h}(t)dt}$$
(17)

If the failure time probability density functions of the two failure modes are dependent, we have:

$$MT_{i}(F_{j}, F_{h}) = t_{i} - \frac{\int_{t_{i-1}}^{t_{i}} Co_{h, j}(f_{h}(t), f_{j}(t))(t - t_{i-1})dt}{\int_{t_{i-1}}^{t_{i}} Co_{h, j}(f_{h}(t), f_{j}(t))dt}$$
(18)

The expected time from the failure of a system because of the j<sup>th</sup> and  $h^{\text{th}}$  failure modes until the time  $t_i$ , given that the failure because of the  $h^{\text{th}}$  failure mode has happened at the  $i^{\text{th}}$  sampling time interval while the failure because of the jth failure mode has happened before the  $i^{th}$  sampling time interval, is:

$$MT_{i}(F_{h}, F_{j}|F_{j}) = t_{i} - \frac{\int_{t_{i-1}}^{t_{i}} f_{h, j|j}(t)(t - t_{i-1})dt}{\int_{t_{i-1}}^{t_{i}} f_{h, j|j}(t)dt}$$
(19)

where  $f_{h,j/h}$  is the conditional failure time probability density function of the  $h^{th}$  and  $j^{th}$  modes given the  $j^{th}$  failure mode. If the two modes are independent:

$$\mathbf{MT}_{i}(F_{h}, F_{i}|F_{i}) = \mathbf{MT}_{i}(F_{h}) \tag{20}$$

Otherwise, we have

$$\mathbf{MT}_{i}(F_{h}, F_{j}|F_{j}) = t_{i} - \frac{\int_{t_{i-1}}^{t_{i}} \frac{\mathbf{Co}_{h,j}(\mathbf{f}_{h}(t), \mathbf{f}_{j}(t))}{\mathbf{f}_{j}(t)} (t - t_{i-1}) dt}{\int_{t_{i-1}}^{t_{i}} \frac{\mathbf{Co}_{h,j}(\mathbf{f}_{h}(t), \mathbf{f}_{j}(t))}{\mathbf{f}_{j}(t)} dt}$$
(21)

Measurement error functions. Assuming a normal distribution of measurement error due to the jth failure mode with mean  $\mu_i$  and standard deviation  $\sigma_i$ , the probability density function of the measurement error is:

$$g_{j}(x) = \frac{1}{\sqrt{2\pi}} \frac{e^{-\frac{(x-\mu_{j})^{2}}{2\sigma_{j}^{2}}}}{\sigma_{j}}$$
(22)

It is assumed that the probability density function  $g_0(x)$  of the measurement error of a system during the reliability state is the unit normal distribution (that is  $\mu_0 = 0$  and  $\sigma_0 = 1$ ).

The probability density function of the so called "intermittent error" is defined as a mixture distribution:

$$g_i(x) = w_j g_i(x) + (1 - w_j) u_0(x)$$
 (23)

where  $\underline{g}_{i}$  is a normal distribution,  $u_{0}$  is a uniform distribution with an arbitrary large interval  $[-\omega,\omega]$  and  $w_i$  is the probability of the "intermittent error" being operative at a particular moment.

The critical measurement error ce(x) is defined as:

$$ce(x) = \begin{cases} 0, |x| \le mte \\ |x| - mte, |x| > mte \end{cases}$$
 (24)

where x is the measurement error.

If we denote with mte the medically acceptable measurement error, the following critical measurement error measures are defined as the sum of the  $d^{th}$  upper and the absolute value of the  $d^{th}$  lower partial moments of the measurement error with reference to the mte and -mte respectively (see Partial moments in Appendix S1):

$$\operatorname{Mce}_{d}(F_{j}) = \left| \int_{-\infty}^{-mte} g_{j}(x)(x+mte)^{d} dx \right| + \int_{mte}^{\infty} g_{j}(x)(x-mte)^{d} dx =$$

$$\int_{-\infty}^{\infty} g_{j}(x)\operatorname{ce}(x)^{d} dx$$
(25)

$$\operatorname{Mce}_{d}(R) = \left| \int_{-\infty}^{-mte} g_{0}(x)(x+mte)^{d} dx \right| + \int_{mte}^{\infty} g_{0}(x)(x-mte)^{d} dx =$$

$$\int_{-\infty}^{\infty} g_{0}(x)\operatorname{ce}(x)^{d} dx$$
(26)

$$\operatorname{Mce}_{d}(F_{j}, F_{h}) = \left| \int_{-\infty}^{-mte} \int_{-\infty}^{\infty} g_{j}(x - y) g_{h}(y) (x + mte)^{d} dy dx \right| + \left| \int_{mte}^{\infty} \int_{-\infty}^{\infty} g_{j}(x - y) g_{h}(y) (x - mte)^{d} dy dx \right|$$

$$= \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} g_{j}(x - y) g_{h}(y) \operatorname{ce}(x)^{d} dy dx$$

$$(27)$$

For d=0 the measures equal the measurement process fraction nonconforming. The normalized the sum of the  $d^{th}$  upper and the absolute value of the  $d^{th}$  lower partial moments of the measurement error with reference to the mte and -mte respectively, for any state S of the system equals (figure 2):

$$NMce_{d}(S) = \begin{cases} (Mce_{d}(S))^{\frac{1}{d}}, d > 0 \\ Mce_{d}(S), d = 0 \end{cases}$$
 (28)

**Quality functions.** Assuming a QC procedure with a single value QC rule with a decision limit l, one control per level and c levels of controls with the same measurement error probability density function, the probability of rejection because of the j<sup>th</sup> failure mode is:

$$\operatorname{Prej}_{c}(F_{j}) = 1 - \left(\int_{-l}^{l} g_{j}(x)dx\right)^{c} \tag{29}$$

Assuming an additive measurement error model, the respective probability of rejection because of the combined  $j^{\text{th}}$  and  $h^{\text{th}}$  failure modes is:

$$\operatorname{Prej}_{c}(F_{j}, F_{h}) = 1 - \left( \int_{-l}^{l} \int_{-\infty}^{\infty} g_{j}(x - y) g_{h}(y) dy dx \right)^{c}$$
(30)

If the probability density functions of the measurement error of the two failure modes are correlated, the respective probability of rejection because of the combined  $f^{\rm th}$  and  $h^{\rm th}$  failure modes is:

### fraction nonconforming

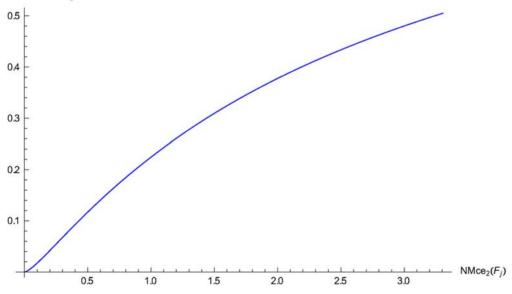


Figure 2. Parametric plot of a critical error measure. Parametric plot of the critical measurement error measure NMce<sub>2</sub>( $F_j$ ), based on the normalized sum of the second upper and the absolute value of the second lower partial moments of the measurement error with reference to mte and -mte respectively, versus the fraction nonconforming, assuming mte = 4.0 and a normal measurement error distribution  $g_j(x)$  with  $\mu_j$  = 0, and  $1 \le \sigma_j \le 6$ . doi:10.1371/journal.pone.0005770.g002

$$\operatorname{Prej}_{c}(F_{j}, F_{h}) = 1 - \left( \int_{-1}^{1} \int_{-1}^{1} g_{j,h}(x, y) dy dx \right)^{c}$$
 (31)

where  $g_{i,h}(x,y)$  is a bivariate probability density function (See Definition of functions assuming multivariate measurement error probability density functions in Appendix S1).

The probability of rejection of the reliability state is:

$$\operatorname{Prej}_{c}(R) = 1 - \left( \int_{-l}^{l} g_{0}(x) dx \right)^{c} = 1 - \left( \frac{1}{\sqrt{2\pi}} \int_{-l}^{l} e^{-\frac{x^{2}}{2}} dx \right)^{c}$$
(32)

**Risk functions.** Using eq. (28) we can define the risk function of a state  $S \neq M$  that during the  $i^{th}$  time interval persists for time  $\tau_i$  as:

$$\operatorname{Lr}_{i,d}(S) = \tau_i \operatorname{NMce}_d(S)$$
 (33)

The residual risk function of the state S, assuming one control per level and c levels of controls is:

$$Lrr_{i,c,d}(S) = (1 - Prej_c(S))Lr_{i,d}(S)$$
(34)

It is assumed that  $\operatorname{Lr}_{i,d}(M) = 0$  and  $\operatorname{Lrr}_{i,e,d}(M) = 0$ .

The risk and residual risk are estimated as risk or residual risk per time interval.

The time independent measures

$$RLr_d(S) = \frac{Lr_{i,d}(S)}{\tau_i} = NMce_d(S)$$
 (35)

and

$$RLrr_{c,d}(S) = \frac{Lrr_{i,c,d}(S)}{\tau_i} = (1 - Prej_c(S))NMce_d(S)$$
 (36)

can be considered as the state risk and residual risk rates. These measures can be used instead of the allowable error based quality measures [3]. For d=0 the risk rate equals the measurement process fraction nonconforming, while the residual risk rate equals the fraction nonconforming given the application of the QC procedure. The risk rate can be used for the definition of the critical-failure modes, and the residual risk rate for the definition of the QC procedures.

**Cost functions.** Assuming the application of the QC procedure at one control per level, at c levels of controls, the QC related cost functions of the states are defined as:

$$C_{i,c}(M) = \frac{2cq + m + t_i - t_{i-1}}{t_i - t_{i-1}}$$
(37)

and for  $S \neq M$ ,

$$C_{i,c}(S) = \frac{cq}{t_i - t_{i-1}}$$
(38)

where q is the cost of each control and its measurement, and m is a maintenance related cost. As cost unit is considered the cost of the analysis of the samples per unit of time in the reliability state.

The QC related cost is estimated as cost per unit of time of each time interval.

# Definitions of the vectors and matrices

It is assumed that the elements of the state vector of an analytical system are the reliability state R, the maintenance state M, the possible critical-failure modes  $F_i$ , and their combinations  $F_i$ ,  $F_{i,...},F_{n}$ . Therefore, the state vector of an analytical system with one failure mode is:

$$\mathbf{s}_1 = [F_1 \quad M \quad R] \tag{39}$$

while the state vector of an analytical system with two failure modes is:

$$\mathbf{s}_2 = [F_1 \quad F_2 \quad (F_1, F_2) \quad M \quad R]$$
 (40)

The respective state probability vectors are:

$$\mathbf{p}_{i}(\mathbf{s}_{1}) = [\operatorname{Ps}_{i}(F_{1}) \quad \operatorname{Ps}_{i}(M) \quad \operatorname{Ps}_{i}(R)]$$
 (41)

$$\mathbf{p}_{i}(\mathbf{s}_{2}) = \begin{bmatrix} \mathbf{P}_{s_{i}}(F_{1}) & \mathbf{P}_{s_{i}}(F_{2}) & \mathbf{P}_{s_{i}}(F_{1}, F_{2}) & \mathbf{P}_{s_{i}}(M) & \mathbf{P}_{s_{i}}(R) \end{bmatrix}$$

$$(42)$$

where  $Ps_i(S)$  the probability of the state S at the end of the  $i^{th}$ sampling time interval.

If  $\mathbf{a} = \mathbf{p}_i(\mathbf{s}_n)$  and  $\mathbf{b} = \mathbf{pc}_i(\mathbf{s}_n | \neg M_i)$ , that is the conditional state probability vector given that the system is not in the maintenance state M at the end of the  $i^{th}$  sampling time interval, where n is the number of the elements of the probability state vectors **a** and **b**, and  $a_k$  and  $b_k$  the  $k^{\text{th}}$  element of each vector, then for  $1 \le k \le n$ :

$$a_k \neq P(M_i) \Rightarrow b_k = \frac{a_k}{1 - P(M_i)} \land a_k = P(M_i) \Rightarrow b_k = 0$$
 (43)

The state transitions of the systems with one and two failure modes could be respectively presented in matrix form as following:

$$\mathbf{T}_{1} = \begin{pmatrix} F_{1} \rightarrow F_{1} & F_{1} \rightarrow M & F_{1} \rightarrow R \\ M \rightarrow F_{1} & M \rightarrow M & M \rightarrow R \\ R \rightarrow F_{1} & R \rightarrow M & R \rightarrow R \end{pmatrix}$$
(44)

and

$$\mathbf{T}_{2} = \begin{pmatrix} F_{1} \rightarrow F_{1} & F_{1} \rightarrow F_{2} & F_{1} \rightarrow (F_{1}, F_{2}) & F_{1} \rightarrow M & F_{1} \rightarrow R \\ F_{2} \rightarrow F_{1} & F_{2} \rightarrow F_{2} & F_{2} \rightarrow (F_{1}, F_{2}) & F_{2} \rightarrow M & F_{2} \rightarrow R \\ (F_{1}, F_{2}) \rightarrow F_{1} & (F_{1}, F_{2}) \rightarrow F_{2} & (F_{1}, F_{2}) \rightarrow (F_{1}, F_{2}) \rightarrow M & (F_{1}, F_{2}) \rightarrow R \\ M \rightarrow F_{1} & M \rightarrow F_{2} & M \rightarrow (F_{1}, F_{2}) & M \rightarrow M & M \rightarrow R \\ R \rightarrow F_{1} & R \rightarrow F_{2} & R \rightarrow (F_{1}, F_{2}) & R \rightarrow M & R \rightarrow R \end{pmatrix} \tag{4.5}$$

The  $\mathbf{T}_1$  and  $\mathbf{T}_2$  are helpful for understanding the definitions of the state transition related matrices.

The state transition probability matrices of systems with one and two failure modes during the ith sampling time interval and before the application of the QC procedure, are respectively (see eqs (6), (9), and (13)):

$$\mathbf{R}_{1,i} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ Pc_i(F_1) & 0 & 1 - Pc_i(F_1) \end{bmatrix}$$
(46)

The state transition probability matrix during the  $i^{th}$  sampling time interval and before the application of the QC procedure, of systems with two independent failure modes is:

The matrices of the normalized state mean times from the state transitions during the  $i^{\rm th}$  sampling time interval and before the application of the QC procedure, for one and two failure modes, are respectively (see eqs (16) to (20)):

$$\mathbf{M}_{1,i} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ \frac{MT_i(F_1)}{t_1 - t_{i-1}} & 0 & 1 - \frac{MT_i(F_1)}{t_i - t_{i-1}} \end{bmatrix}$$
(49)

If the failure modes are independent then:

Assuming one control per level and c levels of controls, the state transition probability matrices because of the application of the QC procedure at the end of the i<sup>th</sup> sampling time interval, of systems with one and two failure states are respectively:

$$\mathbf{Q}_{1,i,c} = \begin{bmatrix} 1 - \text{Prej}_{i,c}(F_1) & \text{Prej}_{i,c}(F_1) & 0\\ 0 & 1 & 0\\ 0 & \text{Prej}_{i,c}(R) & 1 - \text{Prej}_{i,c}(R) \end{bmatrix}$$
(52)

$$\mathbf{Q}_{2,i,c} = \begin{bmatrix} 1 - \operatorname{Prej}_{i,c}(F_1) & 0 & 0 \\ 0 & 1 - \operatorname{Prej}_{i,c}(F_2) & 0 \\ 0 & 0 & 1 - \operatorname{Prej}_{i,c}(F_1, F_2) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$\operatorname{Prej}_{i,c}(F_1) & 0 \\ \operatorname{Prej}_{i,c}(F_2) & 0 \\ \operatorname{Prej}_{i,c}(F_1, F_2) & 0 \\ 1 & 0 \\ \operatorname{Prej}_{i,c}(R) & 1 - \operatorname{Prej}_{i,c}(R) \end{bmatrix}$$
(53)

The risk vectors of systems with one and two failure states are respectively:

$$\mathbf{r}_{i,d}(\mathbf{s}_1) = \begin{bmatrix} \operatorname{Lr}_{i,d}(F_1) & 0 & \operatorname{Lr}_{i,d}(R) \end{bmatrix}$$
 (54)

and

$$\mathbf{r}_{i,d}(\mathbf{s}_2) = \\ [\operatorname{Lr}_{i,d}(F_1) \quad \operatorname{Lr}_{i,d}(F_2) \quad \operatorname{Lr}_{i,d}(F_1, F_2) \quad 0 \quad \operatorname{Lr}_{i,d}(R)]$$
(55)

Assuming one control per level and c levels of controls the QC related cost vectors of systems with one and two failure states, during the t<sup>th</sup> sampling time interval, are respectively:

$$\mathbf{ct}_{i,c}(\mathbf{s}_1) = \begin{bmatrix} C_{i,c}(F_1) & C_{i,c}(M) & C_{i,c}(R) \end{bmatrix}$$
 (56)

and

$$\mathbf{ct}_{i,c}(\mathbf{s}_2) = \\
[\mathbf{C}_{i,c}(F_1) \quad \mathbf{C}_{i,c}(F_2) \quad \mathbf{C}_{i,c}(F_1, F_2) \quad \mathbf{C}_{i,c}(M) \quad \mathbf{C}_{i,c}(R)]$$
(57)

#### Definition of the risk and cost measures

The probabilities of the states at the end of the  $i^{th}$  sampling time interval are estimated from:

- 1. The probabilities of the states at the end of the previous sampling time interval
- The probabilities of the system critical failures during the sampling time interval.
- 3. The probabilities of rejection of the states.

The analytical system state probability vector is estimated by the following recursive equation:

$$\mathbf{p}_{i,c}(\mathbf{s}_n) = \mathbf{p}_{i-1,c}(\mathbf{s}_n) \cdot \mathbf{R}_{n,i} \cdot \mathbf{Q}_{n,i,c}$$
 (58)

The risk of the system at the end of the  $i^{\rm th}$  sampling time interval is estimated from:

- 1. The conditional probabilities of the states at the end of the previous sampling time interval, given that the system is not in the maintenance state.
- The conditional probabilities of the system transition to each state during the i<sup>th</sup> sampling time interval, given that this transition has not happened during the previous sampling time intervals.
- 3. The conditional mean times of each state during the *i*<sup>th</sup> sampling time interval, given that the state transition has happened during this sampling time interval.
- 4. The normalized sum of the d<sup>th</sup> upper and the absolute value of the d<sup>th</sup> lower partial moments of the measurement error with reference to the mte and -mte respectively.

The residual risk of the system at the end of the  $i^{th}$  sampling time interval is estimated from:

- 1. The risk of the states of the system at the end of the  $i^{\rm th}$  sampling time interval.
- 2. The probabilities of rejection of the states.

Therefore, the following risk, residual risk, and QC related cost measures are defined respectively as:

$$r_{n,i,c,d} = \mathbf{pc}_{i-1,c}(\mathbf{s}_n | \neg M) \cdot (\mathbf{R}_{n,i} \bullet \mathbf{M}_{n,i}) \cdot \mathbf{r}_{i,d}(\mathbf{s}_n)^{\mathrm{T}}$$
(59)

$$rr_{n,i,c,d} = \mathbf{pc}_{i-1,c}(\mathbf{s}_n | \neg M) \cdot (\mathbf{R}_{n,i} \bullet \mathbf{M}_{n,i}) \cdot \mathbf{Q}_{n,i,c} \cdot \mathbf{r}_{i,d}(\mathbf{s}_n)^{\mathrm{T}}$$
 (60)

$$ct_{n,i,c} = \mathbf{pc}_{n,i-1,c}(\mathbf{s}_n | \neg M) \cdot \mathbf{R}_{n,i} \cdot \mathbf{Q}_{n,i,c} \cdot \mathbf{ct}_{i,c}(\mathbf{s}_n)^{\mathrm{T}}$$
(61)

where n denotes the number of the failure modes, i the i<sup>th</sup> sampling time interval, c the levels of the controls, and d the d<sup>th</sup> upper and lower partial moments of the measurement error with reference to mte and -mte respectively.

The operator • is the entry wise or Hadamard product operator. Therefore, if  $\mathbf{C} = \mathbf{A} \bullet \mathbf{B}$ , then  $c_{ij} = a_{ij} \cdot b_{ij}$ . The operator  $^{\mathrm{T}}$  is the transpose operator.

The risk and the residual risk measures of the system are estimated as risk and residual risk per time interval while the expected QC related cost of the system is estimated as cost per unit of time.

# Definition of the measures of the performance of the algorithm

The following measures are used to evaluate the results of the consecutive application of the algorithm, assuming n critical-failure modes, one control per level and c levels of controls, a risk function based on the normalized sum of the  $d^{th}$  upper and the absolute value of the  $d^{th}$  lower partial moments of the measurement error with reference to mte and -mte respectively, initial time  $t_0$  and initial states probability vector  $\mathbf{p}(\mathbf{s}_n)$ :

1. The mean time of the application of the algorithm until the system enters the maintenance state, of a series of up to *k* sampling time intervals, that equals:

$$\frac{1}{t_n(t_0, \mathbf{p}_0(\mathbf{s}_n), k)} = \frac{\sum_{i=1}^{k} (t_i - t_0) (\operatorname{Ps}_{n,i}(M) - \operatorname{Ps}_{n,i-1}(M))}{\operatorname{Ps}_{n,k}(M)}$$
(62)

2. The mean number of sampling time intervals until the system enters the maintenance state, of a series of up to *k* sampling time intervals. This measure is an estimate of the average run length and equals:

$$\frac{1}{v_n(t_0, \mathbf{p}_0(\mathbf{s}_n), k)} = \frac{\sum_{i=1}^{k} i(P\mathbf{s}_{n,i}(M) - P\mathbf{s}_{n,i-1}(M))}{P\mathbf{s}_{n,k}(M)}$$
(63)

3. The mean length of the sampling time interval, of a series of up to *k* sampling time intervals that equals:

$$\overline{\Delta t_n(t_0, \mathbf{p}_0(\mathbf{s}_n), k)} = \frac{\overline{t_n(t_0, \mathbf{p}(\mathbf{s}_n), k)}}{v_n(t_0, \mathbf{p}(\mathbf{s}_n), k)}$$
(64)

4. The mean residual risk measure (see eq. (60)) per time interval of a series of up to k sampling time intervals that equals:

$$\overline{rr_{n,c,d}(t_0, \mathbf{p}_0(\mathbf{s}_n), k)} = \frac{\sum_{i=1}^{k} \sum_{j=1}^{i} rr_{n,j,c,d}(P\mathbf{s}_{n,i}(M) - P\mathbf{s}_{n,i-1}(M))}{\overline{v_n(t_0, \mathbf{p}_0(\mathbf{s}_n), k)} P\mathbf{s}_{n,k}(M)}$$
(65)

5. The mean expected QC related cost per time unit measure (see eq. (61)) of a series of up to k sampling time intervals that

Table 1. Parameters of the analytical systems.

Parameter failure modes	Notation	Analytical System I	Analytical System II	Analytical System III	
	F <sub>j</sub>			F <sub>1</sub>	F <sub>2</sub>
parameters of the general distribution	$\alpha_j$	0.5	0.5	0.5	0.5
	$eta_j$	1	1	1	1
	$\gamma_j$	0.8	0.9	0.8	0.9
	$\theta_{j}$	0.001	0.0001	0.001	0.0001
	$\lambda_j$	0.001	0.001	0.001	0.001
mean time to failure	MT(F <sub>j</sub> )	1956.98	13901.4	1956.98	13901.40
parameters of the error distribution	$\mu_j$	0	0	0	0
	$\sigma_{j}$	3	5	3	5
acceptable measurement error	mte	4	4	4	
acceptable residual risk	rr <sub>n,i,2,2</sub>	0.4	0.4	0.4	
levels of controls	с	2	2	2	
controls per level		1	1	1	
maintenance cost	m	4	4	0.4	
QC sample cost	9	0.5	0.5	0.05	
moment of risk measures	d	2	2	2	
upper bound of risk rate measure	RLr <sub>2</sub> (S)	0.4	0.4	0.4	
upper bound of residual risk rate measure	RLrr <sub>2</sub> ,2(S)	0.4	0.4	0.4	
QC rules decision limit	Ī	3.18	2.68	2.68	

The parameters of the analytical systems I to III. doi:10.1371/journal.pone.0005770.t001

equals:

$$\overline{ct_{n,c}(t_0, \mathbf{p}_0(\mathbf{s}_n))} = \sum_{i=1}^{k} \sum_{j=1}^{i} ct_{n,j,c}(t_j - t_{j-1}) (\operatorname{Ps}_{n,i}(M) - \operatorname{Ps}_{n,i-1}(M)) \over \overline{t_n(t_0, \mathbf{p}_0(\mathbf{s}_n), k)} \operatorname{Ps}_{k,i}(M)}$$
(66)

# About the maintenance state

Although the model can be expanded to include more maintenance related states, as well as a maintenance related state transition probability matrix, it may be applied as it is if we assume that during the maintenance state the system is checked and if there is a critical failure it is repaired. Then the algorithm is applied again, assuming an updated initial states probability vector with the reliability state as the initial state of the system and an updated initial time  $t_0 > 0$ . If the system has been repaired, then the same or revised critical-failure time probability density functions are used. If the system has not been repaired because no critical failure has been found, then the same critical-failure time probability density functions are used.

# Simulations

To explore the mean residual risk per sampling interval and the mean expected QC related cost per time unit using either optimal or predefined QC sampling time intervals I simulated the three analytical systems I to III presented in table 1.

The three simulated analytical systems could be clinical chemistry analyzers, measuring for example the serum glucose or cholesterol concentration, with zero bias and coefficient of variation equal to 2.5%, assuming a medically acceptable measurement error equal to 10%.

# Simulations of consecutive applications of the algorithm

**Relation between residual risk and cost.** To explore the relation between the mean residual risk per sampling interval and the mean expected QC related cost per time unit when a QC procedure is applied repeatedly until the system enters the maintenance state, I estimated the mean residual risk  $\overline{rr_{n,c,d}(t_0, \mathbf{p}_0(\mathbf{s}_n), k)}$  (see eq.(65)) and the mean expected cost measure  $ct_{n,c}(t_0, \mathbf{p}_0(\mathbf{s}_n), k)$  (see eq. (66)) of the analytical systems I to III (see table 1), assuming:

- 1. Constant length sampling time intervals  $\Delta t_i$ :
  - a. from 4 to 96 time units, using 4 time units steps,
  - b. from 8 to 192 time units, using 8 time units steps, and
  - c. from 4 to 96 time units, using 4 time units steps, respectively.
- 2. Single value QC rules applied at one control per level, at two levels of controls, with decision limits l from 2.0 to 4.0  $\sigma_0$  using 0.1  $\sigma_0$  steps.
- 3. The reliability state R as the initial state of the systems.
- 4. Initial times  $t_0 = 0$  and  $t_0 = \frac{1}{2}$ MTCF, where MTCF is the mean time to critical failure of each analytical system.

To estimate the measures I ran the simulations while  $Ps_k$  (M) $\leq$ 0.99, where  $Ps_k$  (M) is the probability of the maintenance state after the  $k^{th}$  consecutive application of the algorithm.

**Estimation of optimal QC sampling intervals.** I ran six illustrative simulations (Ia to IIIb, see table 2), to demonstrate the dynamics of the consecutive application of the algorithm until the

Table 2. Statistics of the simulations la to IIIb.

		Simulation	Simulation	Simulation 	Simulation	Simulation	Simulation
	Notation	la	lb	lla	IIb	Illa	IIIb
analytical system		1	1	II	II	III	III
initial time	$t_0$	0	978.49	0	6950.70	0	857.79
mean time until the system enters the maintenance state	$\overline{t_n(t_0,\mathbf{p}_0(\mathbf{s}_n),k)}$	1758.62	1170.14	4529.57	3818.93	1010.45	757.75
mean number of sampling time intervals until the system enters the maintenance state	$\overline{v_n(t_0,\mathbf{p}_0(\mathbf{s}_n),k)}$	65.22	54.56	51.95	49.15	42.52	39.34
mean sampling time interval length	$\overline{\Delta t_n(t_0,\mathbf{p}_0(\mathbf{s}_n),k)}$	26.96	21.44	87.19	77.69	23.77	19.26
mean residual risk per sampling time interval	$rr_{n,c,d}(t_0,\mathbf{p}_0(\mathbf{s}_n),k)$	0.400	0.400	0.400	0.400	0.206	0.199
mean expected QC related cost per time unit	$\overline{ct_{n,c}(t_0,\mathbf{p}_0(\mathbf{s}_n),k)}$	0.053	0.057	0.031	0.031	0.027	0.030

The statistics of the simulations la to IIIb. The means were estimated for  $Ps_k(M) \ge 0.99$ . doi:10.1371/journal.pone.0005770.t002

system enters the maintenance state. I ran two simulations for each analytical system of the table 1 assuming initial times  $t_0 = 0$  and  $t_0 = \frac{1}{2}$ MTCF respectively, and the reliability state R as the initial state of the systems.

The acceptable residual risk  $m_{n,i,2,2}$  was set to 0.4 (see eq. 58). The decision limit l of the QC rule of each simulation was defined so that  $\mathrm{RLr}_d$  (S)  $\leq$  0.4 (see eq.(36)) for any state of the respective analytical system. The cost measure to be minimized was the  $ct_{n,i,2}$  (see eq. (61)). To estimate the parameters I ran the simulations while  $\mathrm{Ps}_k$  (M)  $\leq$  0.99.

For each simulation the measures of the eqs (62) to (66) were estimated.

# Monte Carlo simulations of single application of the algorithm

In addition I ran three Monte Carlo simulations for each analytical system (see table 3), assuming:

- 1. Random initial time  $t_0$ ,  $0 \le t_0 \le MTCF$ .
- 2. Initial state probability vector  $\mathbf{p}_0(\mathbf{s}_n)$  for each initial time  $t_0$  with (see eqs (41) and (42)):

- a.  $\operatorname{Ps}_0(F_1) = \int\limits_0^{t_0} \operatorname{f}_1(t) dt$ ,  $\operatorname{Ps}_0(M) = 0$ , and  $\operatorname{Ps}_0(R) = 1 \operatorname{Ps}_0(F_1)$ , for the Monte Carlo simulations I and II.
- b.  $\operatorname{Ps}_0(F_1) = \int_0^{t_0} f_1(t)dt$ ,  $\operatorname{Ps}_0(F_2) = \int_0^{t_0} f_2(t)dt$ ,  $\operatorname{Ps}_0(F_1, F_2) = \left(\int_0^{t_0} f_1(t)dt\right) \left(\int_0^{t_0} f_2(t)dt\right)$ ,  $\operatorname{Ps}_0(M) = 0$ , and  $\operatorname{Ps}_0(R) = 1 \operatorname{Ps}_0(F_1) \operatorname{Ps}_0(F_2) + \operatorname{Ps}_0(F_1, F_2)$ , for the Monte Carlo simulation III.

For each analytical system 1000 initial times  $t_0$  were generated. Then for each initial time  $t_0$ , after a single application of the algorithm, the residual risk measure  $r_{n,1,2,2}$  and the expected QC related cost measure  $ct_{n,1,2}$  (see eqs (60) and (61)) were estimated with QC sampling time intervals  $\Delta t_1$ :

- a. Estimated to be optimal
- b. With predefined length, from 1 to 120 time units, using 1 time unit steps.

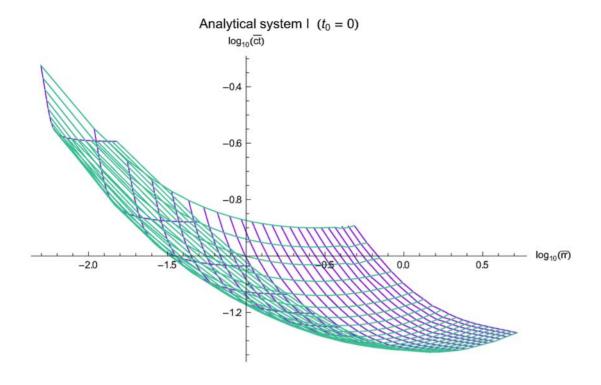
For each initial time  $t_0$  the expected QC related cost per time unit measure of the predefined QC sampling intervals with

Table 3. Statistics of the Monte Carlo simulations I to III.

	Notation	Monte Carlo Simulation I	Monte Carlo Simulation II	Monte Carlo Simulation III	
analytical system		ı	II	III	
mean initial time	$\overline{t_0}$	493.19	3502.57	424.79	
mean initial state probability vector	$\overline{\mathbf{p}_0(\mathbf{s}_n)}$	[0.084 0 0.926]	[0.123 0 0.877]	[0.069 0.022 0.002 0 0.907]	
mean optimal QC sampling time interval length	$\overline{\Delta t_1}$	8.29	6.22	20.07	
mean residual risk measure of the optimal QC sampling time intervals	$\overline{rr_{n,1,2,2}}$	0.400	0.400	0.363	
mean expected QC related cost measure of the optimal QC sampling time intervals	$\overline{ct_{n,1,2}}$	0.165	0.351	0.086	

The statistics of the estimated optimal QC sampling time intervals of the Monte Carlo simulations I to III. The means were estimated for 1000 random initial times  $t_0$ , with  $0 \le t_0 \le MTCF$ .

doi:10.1371/journal.pone.0005770.t003



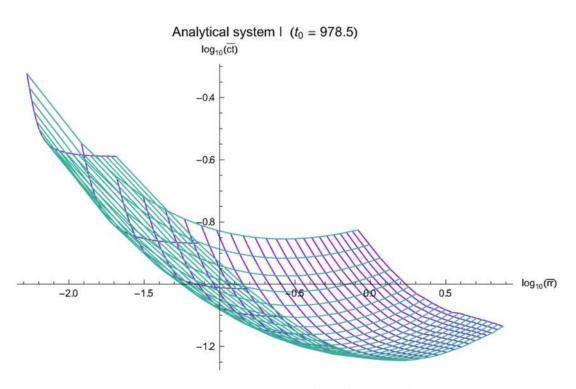
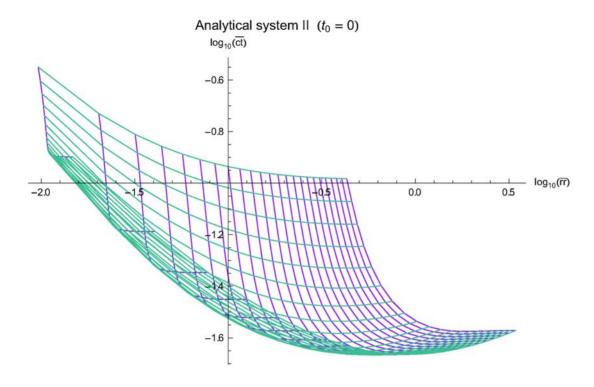


Figure 3. The mean residual risk versus the mean expected QC related cost of the analytical system I. The mean residual risk measure  $\overline{rt_{1,2,2}(t_0, p_0(s_1), k)}$  versus the mean expected QC related cost measure  $\overline{\operatorname{ct}_{1,2}(t_0, p_0(s_1), k)}$  of the analytical system I, assuming initial times  $t_0 = 0$  (upper plot) and  $t_0 = 978.5$  (lower plot), the reliability state as the initial state, constant sampling time interval length  $\Delta t_i$  from 4 to 96 time units, and single value QC rules applied at two levels of controls, with decision limit I from 2.0 to 4.0  $\sigma_0$ . Both means were estimated for  $Ps_k$  (M) $\geq$ 0.99. Each purple line joins the points with the same QC sampling time interval length  $\Delta t_i$  and each light blue line joins the points with the same decision limit I. The  $\Delta t_i$  is increasing from left to right, while the I is increasing from up down. doi:10.1371/journal.pone.0005770.g003



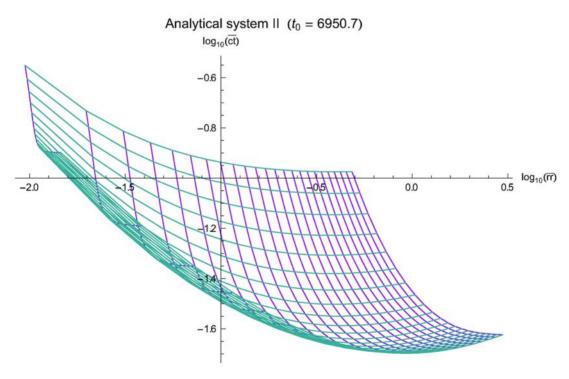
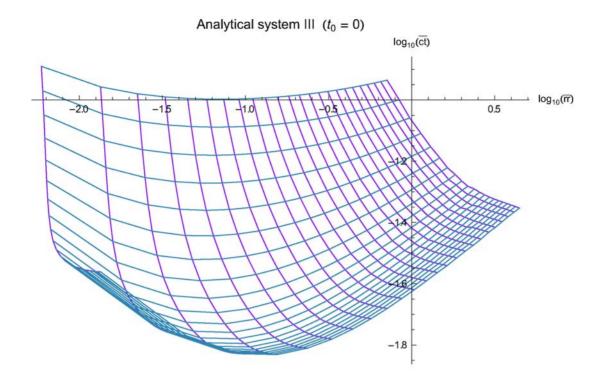


Figure 4. The mean residual risk versus the mean expected QC related cost of the analytical system II. The mean residual risk measure  $\overline{r_{1,2,2}(t_0, p_0(s_1), k)}$  versus the mean QC related cost measure  $\overline{c_{1,2}(t_0, p_0(s_1), k)}$  of the analytical system of the simulations II, assuming initial times  $t_0 = 0$  (upper plot) and  $t_0 = 6950.7$  (lower plot), the reliability state as the initial state, constant sampling time interval length  $\Delta t_i$  from 8 to 192 time units, and single value QC rules applied at two levels of controls, with decision limit l from 2.0 to 4.0  $\sigma_0$ . Both means were estimated for  $Ps_k(M) \ge 0.99$ . Each purple line joins the points with the same QC sampling time interval length  $\Delta t_i$  and each light blue line joins the points with the same decision limit l. The  $\Delta t_i$  is increasing from left to right, while the l is increasing from up down. doi:10.1371/journal.pone.0005770.g004



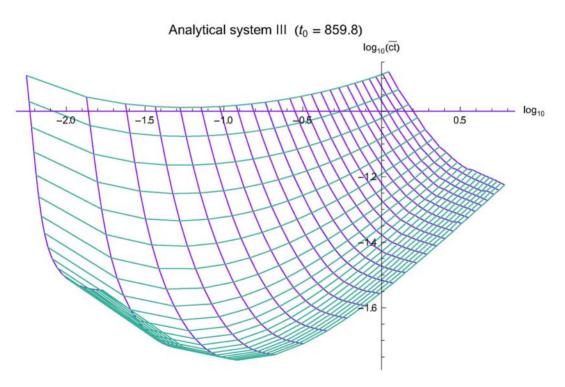
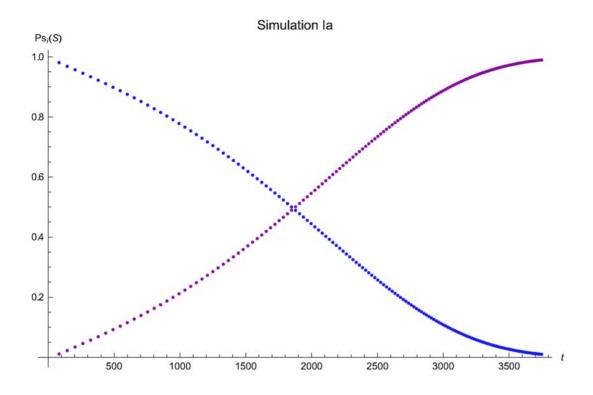


Figure 5. The mean residual risk versus the mean expected QC related cost of the analytical system III. The mean residual risk measure  $r_{2,2,2}(t_0, p_0(s_2), k)$  versus the mean QC related cost measure  $c_{2,2}(t_0, p_0(s_2), k)$  of the analytical system of the simulations III, assuming initial times  $t_0 = 0$  (upper plot) and  $t_0 = 857.8$  (lower plot), the reliability state as the initial state, constant sampling time interval length  $\Delta t_i$  from 4 to 96 time units, and single value QC rules applied at two levels of controls, with decision limit I from 2.0 to 4.0  $\sigma_0$ . Both means were estimated for  $P_{s_k}(M) \ge 0.99$ . Each purple line joins the points with the same QC sampling time interval length  $\Delta t_i$  and each light blue line joins the points with the same decision limit I. The  $\Delta t_i$  is increasing from left to right, while the I is increasing from up down. doi:10.1371/journal.pone.0005770.g005



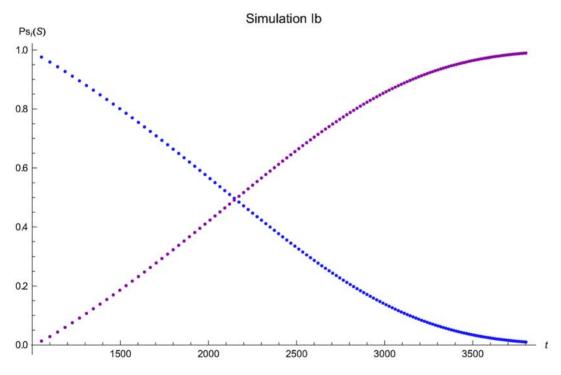
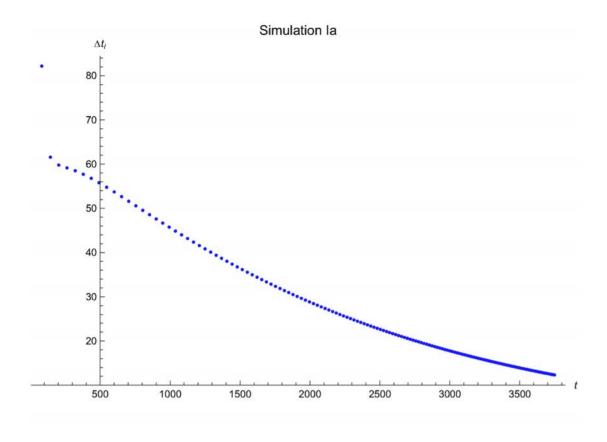


Figure 6. The probabilities of the reliability and maintenance states versus the time of the simulations la and lb. The probabilities of the reliability (R) and maintenance (M) states versus the time t of the simulations la (upper plot) and lb (lower plot), assuming initial times  $t_0 = 0$  and  $t_0 = 978.5$  respectively and the reliability state as the initial state. doi:10.1371/journal.pone.0005770.g006



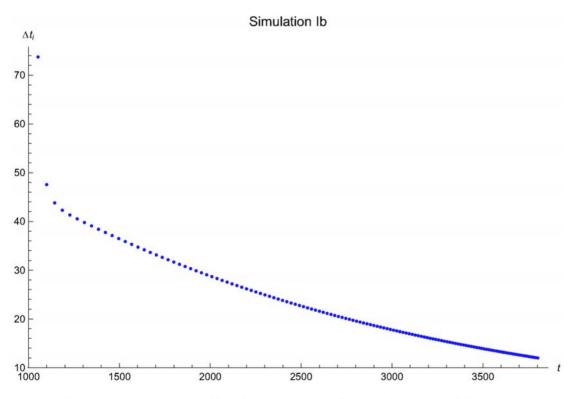
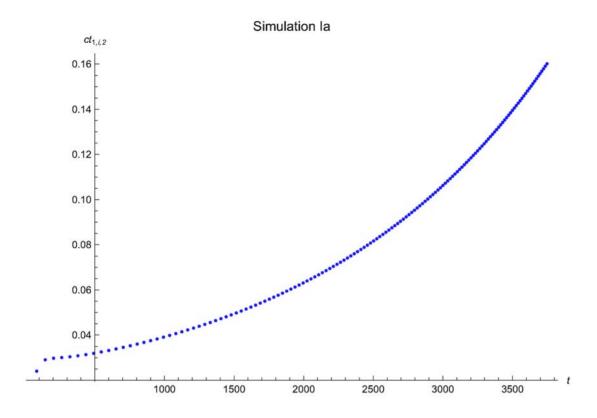


Figure 7. The QC sampling time interval length versus the time of the simulations Ia and Ib. The length of the QC sampling time interval length  $\Delta t_i$  versus the time t of the simulations Ia (upper plot) and Ib (lower plot), assuming initial times  $t_0$ =0 and  $t_0$ =978.5 respectively and the reliability state as the initial state. The  $\Delta t_i$  was estimated assuming that the system had not entered the maintenance state for  $t < t_{i-1}$ . doi:10.1371/journal.pone.0005770.g007



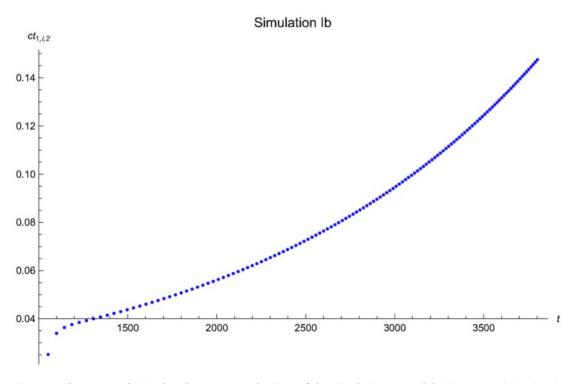
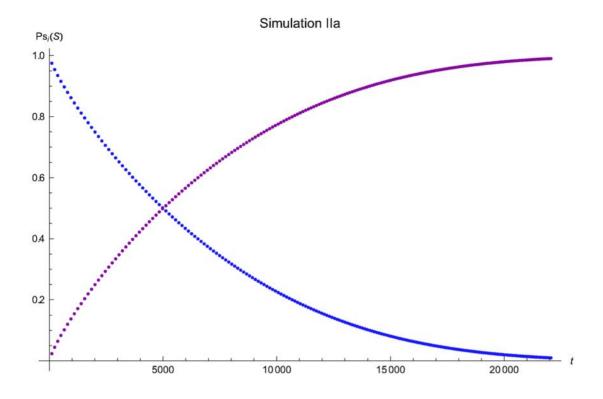


Figure 8. The expected QC related cost versus the time of the simulations la and lb. The expected QC related cost measure  $ct_{1,i,2}$  versus the time t of the simulations la (upper plot) and lb (lower plot), assuming initial times  $t_0$  = 0 and  $t_0$  = 978.5 respectively and the reliability state as the initial state. The  $ct_{1,i,2}$  was estimated assuming that the system had not entered the maintenance state for  $t < t_{i-1}$ . doi:10.1371/journal.pone.0005770.g008



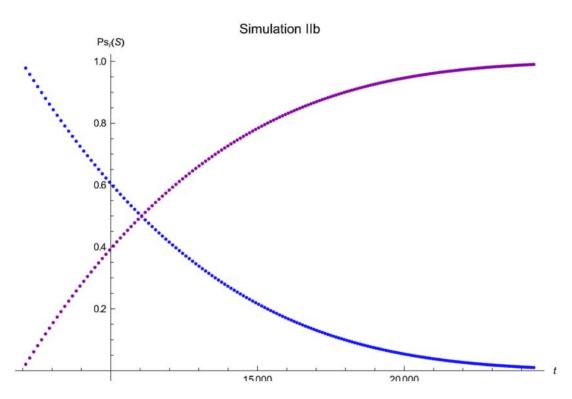
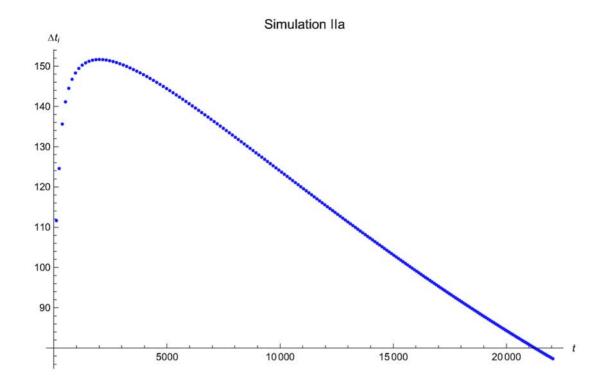


Figure 9. The probabilities of the reliability and maintenance states versus the time of the simulations IIa and IIb. The probabilities of the reliability (R) and Maintenance (M) states versus the time t of the simulations IIa (upper plot) and IIb (lower plot), assuming initial times  $t_0$  = 0 and  $t_0$  = 6950.7 respectively and the reliability state as the initial state. doi:10.1371/journal.pone.0005770.g009



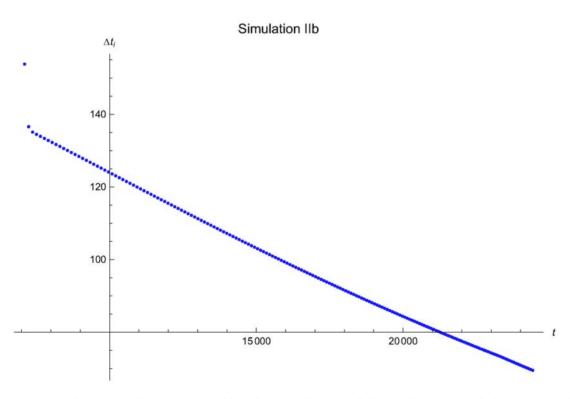
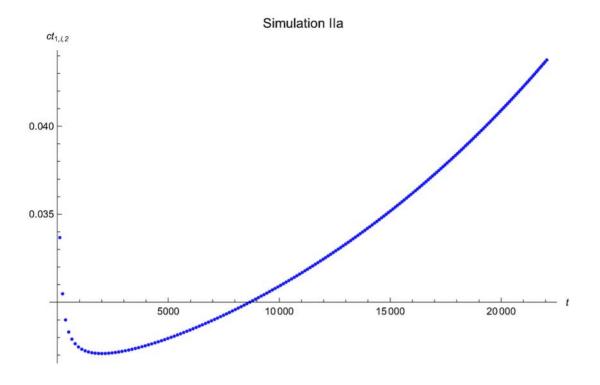


Figure 10. The QC sampling time interval length versus the time of the simulations IIa and IIb. The length of the QC sampling time interval length  $\Delta t_i$  versus the time t of the simulations IIa (upper plot) and IIb (lower plot), assuming initial times  $t_0$  = 0 and  $t_0$  = 6950.7 respectively and the reliability state as the initial state. The  $\Delta t_i$  was estimated assuming that the system had not entered the maintenance state for  $t < t_{i-1}$ . doi:10.1371/journal.pone.0005770.g010



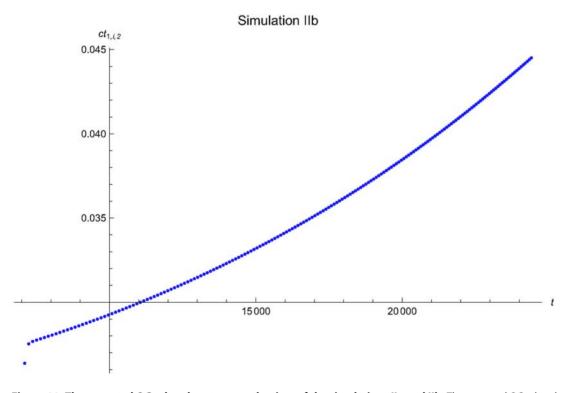
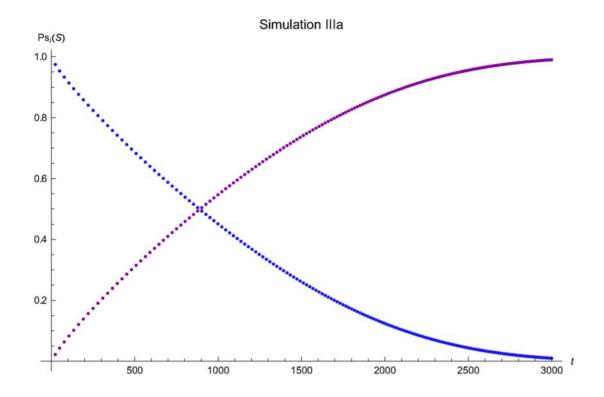


Figure 11. The expected QC related cost versus the time of the simulations IIa and IIb. The expected QC related cost measure  $ct_{1,i,2}$  versus the time t of the simulations IIa (upper plot) and IIb (lower plot), assuming initial times  $t_0 = 0$  and  $t_0 = 6950.7$  respectively and the reliability state as the initial state. The  $ct_{1,i,2}$  was estimated assuming that the system had not entered the maintenance state for  $t < t_{i-1}$ . doi:10.1371/journal.pone.0005770.g011



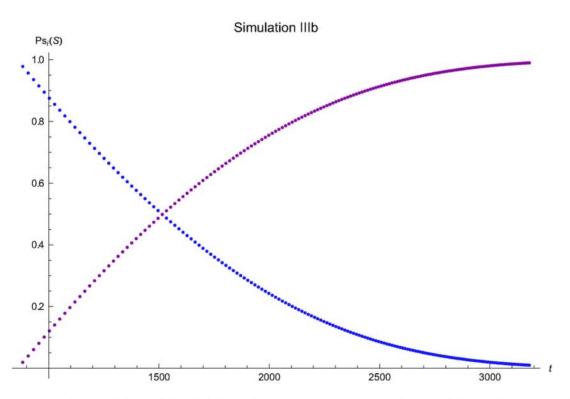
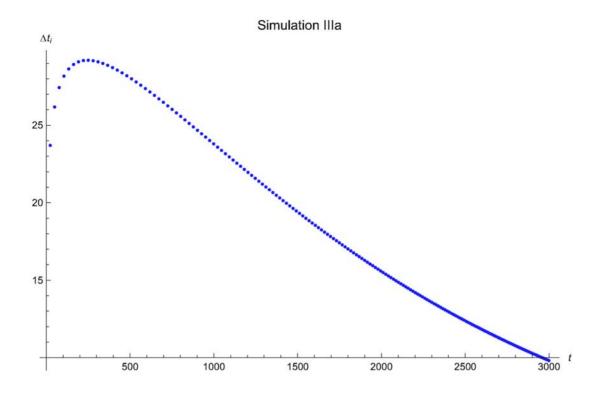


Figure 12. The probabilities of the reliability and maintenance states versus the time of the simulations IIIa and IIIb. The probabilities of the reliability (R) and maintenance (M) states versus the time t of the simulations IIIa (upper plot) and IIIb (lower plot), assuming initial times  $t_0 = 0$  and  $t_0 = 857.8$  respectively and the reliability state as the initial state. doi:10.1371/journal.pone.0005770.g012



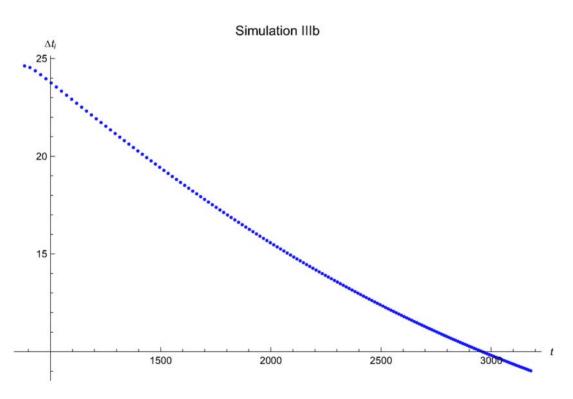
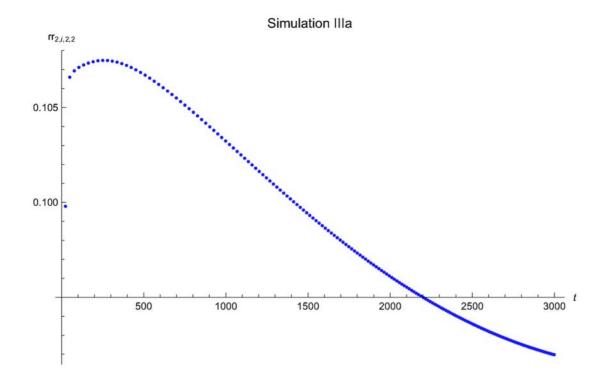


Figure 13. The QC sampling time interval length versus the time of the simulations IIIa and IIIb. The length of the QC sampling time interval length  $\Delta t_i$  versus the time t of the simulations IIIa (upper plot) and IIIb (lower plot), assuming initial times  $t_0 = 0$  and  $t_0 = 857.8$  respectively and the reliability state as the initial state. The  $\Delta t_i$  was estimated assuming that the system had not entered the maintenance state for  $t < t_{i-1}$ . doi:10.1371/journal.pone.0005770.g013



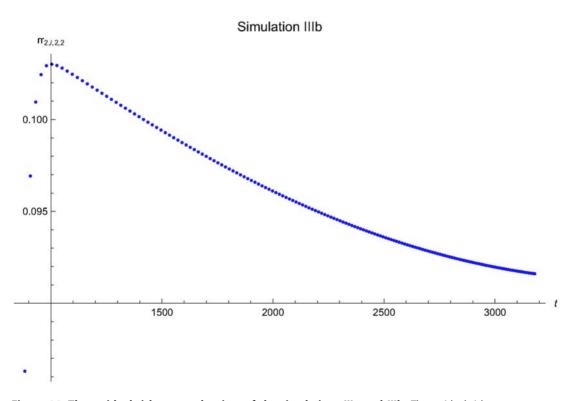
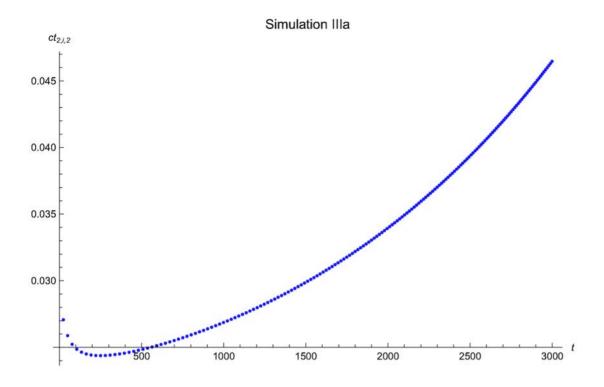


Figure 14. The residual risk versus the time of the simulations IIIa and IIIb. The residual risk measure  $rr_{2,i,2,2}$  versus the time t of the simulations IIIa (upper plot) and IIIb (lower plot), assuming initial times  $t_0 = 0$  and  $t_0 = 857.8$  respectively and the reliability state as the initial state. The  $rr_{2,i,2,2}$  was estimated assuming that the system had not entered the maintenance state for  $t < t_{i-1}$ . doi:10.1371/journal.pone.0005770.g014



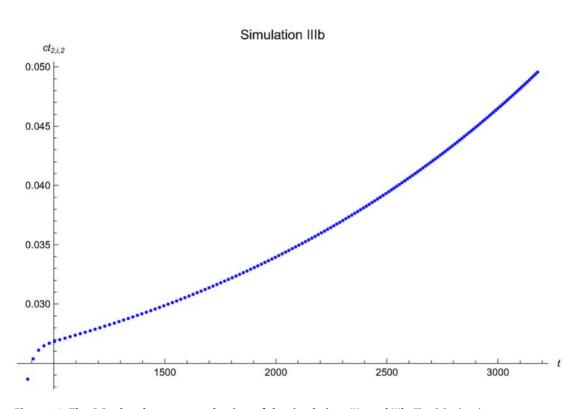


Figure 15. The QC related cost versus the time of the simulations IIIa and IIIb. The QC related cost measure  $ct_{2,j,2}$  versus the time t of the simulations Illa (upper plot) and Illb (lower plot), assuming initial times  $t_0 = 0$  and  $t_0 = 857.8$  respectively and the reliability state as the initial state. The  $ct_{2,i,2}$  was estimated assuming that the system had not entered the maintenance state for  $t < t_{i-1}$ . doi:10.1371/journal.pone.0005770.g015

acceptable residual risk measure was compared with the respective measure of the QC sampling interval estimated to be optimal.

For each predefined QC sampling interval, with acceptable residual risk measures for all the initial times  $t_0$ , the mean measure  $\overline{ct_{n,1,2}}$  for all the initial times  $t_0$  was compared with the respective mean measure of the QC sampling intervals estimated to be optimal, using the paired Students t-test.

#### Results

Simulations of consecutive applications of the algorithm Relation between residual risk and cost. The figures 3, 4

and 5 present the mean residual risk measure  $rr_{n,2,2}(t_0, \mathbf{p}_0(\mathbf{s}_n), k)$ versus the mean expected QC related cost measure  $\overline{\operatorname{ct}_{n,2}(t_0,\,\mathbf{p}_0(\mathbf{s}_n),\,k)}$  of the analytical systems I to III, assuming initial times  $t_0 = 0$  (upper plots) and  $t_0 = \frac{1}{2}$  MTCF (lower plots). Each purple line joins the points with QC sampling time interval of the same length  $\Delta t_i$  and each light blue line joins the points with the same decision limit l. The  $\Delta t_i$  is increasing from left to right, while the l is increasing from up down. The relation between the two measures is nonlinear.

Estimation of optimal QC sampling intervals. The results of the simulations estimating the optimal QC intervals during the consecutive applications of the algorithm are presented in the table 2 and in the following figures:

- 1. Simulations Ia (upper plots) and IIa (lower plots): figures 6, 7,
- 2. Simulations IIa (upper plots) and IIb (lower plots): figures 9, 10,
- 3. Simulations IIIa (upper plots) and IIIb (lower plots): figures 12, 13, 14, and 15.

In all these simulations, an acceptable residual risk was

The table 2 presents the estimated measures of the eqs (62) to (66) for each simulation.

The figures 6, 9, and 12 present the probabilities of the reliability (R) and maintenance (M) states versus the time t of the simulations Ia, IIa, and IIIa (upper plots) and Ib, IIb, IIIb (lower plots), assuming initial times  $t_0 = 0$  and  $t_0 = \frac{1}{2}$ MTCF respectively.

The figures 7, 10, and 13 present the length of the QC sampling time interval  $\Delta t_i$  versus the time t of the simulations Ia, IIa, and IIIa (upper plots) and Ib, IIb, and IIIb (lower plots), assuming initial times  $t_0 = 0$  and  $t_0 = \frac{1}{2}$ MTCF respectively. In all simulations the length the QC sampling time intervals is variable. In general the length of the QC sampling time intervals is decreasing with the time t. It is increasing with t for  $0 < t \le 2032.23$  time units in the simulation IIa (see fig. 10) and for  $0 \le t \le 248.43$  time units in the simulation IIIa (see fig. 13).

The figures 8, 11, and 15 present the expected QC related cost measure  $ct_{n,i,2}$  versus the time t of the simulations Ia, IIa, and IIIa (upper plots) and Ib, IIb, and IIIb (lower plots), assuming initial times  $t_0 = 0$  and  $t_0 = \frac{1}{2}$ MTCF respectively. In general, the ct<sub>1,i,2</sub> is increasing with the time t. It is decreasing with t for  $0 \le t \le 2032.23$ time units in the simulation IIa (see fig. 11) and for  $0 \le t \le 248.43$ time units in the simulation IIIa (see fig. 15).

The figure 14 presents the residual risk measure  $r_{2,i,2,2}$  versus the time t of the simulations IIIa (upper plot) and IIIb (lower plot), assuming initial times  $t_0 = 0$  and  $t_0 = \frac{1}{2}$ MTCF respectively. A remarkable result of these two simulations is that  $r_{2,i,2,2} < 0.4$ .

# Monte Carlo simulations of single application of the algorithm

The table 3 presents the parameters of the Monte Carlo Simulations I to III of single application of the algorithm and the statistics of the estimated optimal QC sampling time intervals. The figures 16, 17 and 18 present the mean residual risk measure  $\overline{rr_{n,1,2,2}}$  (upper plots) and the mean expected QC related cost measure  $\overline{ct_{n,1,2}}$  (lower plots) versus the length of the predefined QC sampling time intervals  $\Delta t_1$  of the Monte Carlo Simulations I to II. The x-axes origins are set to the mean length of the QC sampling time intervals estimated to be optimal. The y-axes origins are set respectively to the mean residual risk measure  $\overline{rr_{1,1,2,2}}$  and the mean expected QC related cost measure  $\overline{ct_{1,1,2}}$  of the QC sampling time intervals estimated to be optimal. The mean residual risk measure  $\overline{rr_{n,1,2,2}}$  is increasing with the length  $\Delta t_1$  of the predefined QC sampling time intervals. In general, the mean expected QC related cost measure  $\overline{ct_{n,1,2}}$  is decreasing with the length  $\Delta t_1$  of the predefined QC sampling time intervals. It is increasing for  $34 < \Delta t_1 \le 120$  time units in the Monte Carlo simulation III.

For each initial time  $t_0$ :

- 1. An optimal QC sampling time interval with acceptable residual risk measure  $r_{n,1,2,2}$  was estimated.
- 2. The expected QC related cost measure  $ct_{n,1,2}$  of that interval was less than the respective measure of each predefined QC sampling interval with acceptable residual risk measure.
- 3. The difference between the length of the predefined QC sampling interval with acceptable residual risk measure  $r_{n,1,2,2}$ and minimal QC related cost measure  $ct_{n,1,2}$ , and the QC sampling time interval estimated to be optimal, was less than one time unit.

The predefined QC sampling intervals  $\Delta t_1$  with acceptable residual risk measure  $r_{n,1,2,2}$  for all the initial times  $t_0$  were:

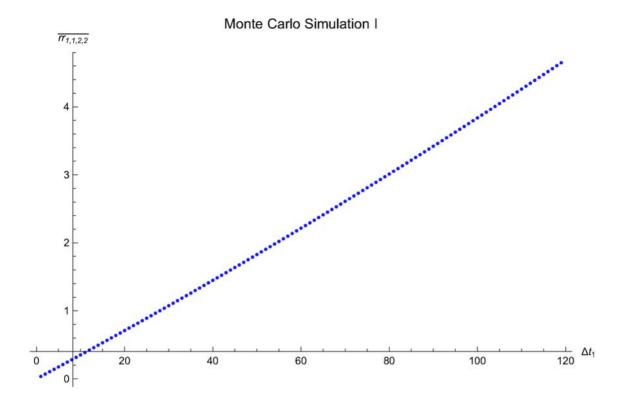
- 1. From 1 to 5 time units for the Monte Carlo simulation I.
- 2. From 1 to 4 time units for the Monte Carlo simulation II.
- 3. From 1 to 11 time units for the Monte Carlo simulation III.

The mean measure  $\overline{ct_{n,1,2}}$  of each of the above predefined QC sampling intervals for all the initial times  $t_0$  was greater than the respective mean measure of the QC sampling intervals estimated to be optimal, with  $p < 10^{-450}$ . Therefore, in these simulations the proposed method for estimating the QC sampling time intervals outperformed the methods with predefined time intervals.

# Discussion

The algorithm I developed offers an insight in the relationship among a QC procedure, the reliability of an analytical system, the risk of the measurement error and the QC related cost. Furthermore, it demonstrates a method for the rational estimation of the QC sampling time intervals of analytical systems with an arbitrary number of failure modes. Therefore, given the reliability analysis of an analytical system, the risk analysis of the measurement error and a QC procedure, there is an optimal QC sampling time interval approach that can sustain an acceptable residual risk, while minimizes the QC related cost.

The needed quantitative fault tree analysis and the estimation of the critical-failure time probability density functions of the modern analytical systems may be very complex. It is possible though to derive at least upper bounds of them using techniques handling uncertainty [18]. A more complex issue is the estimation of the



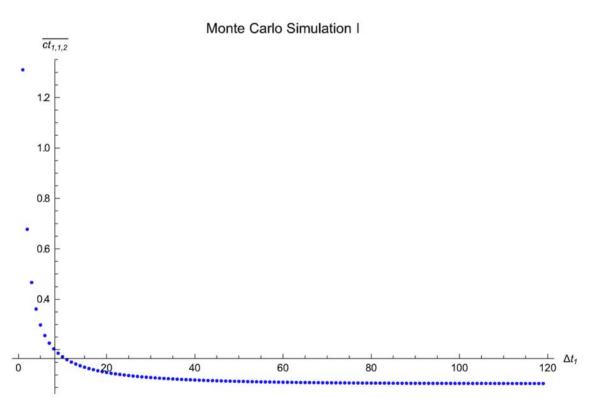
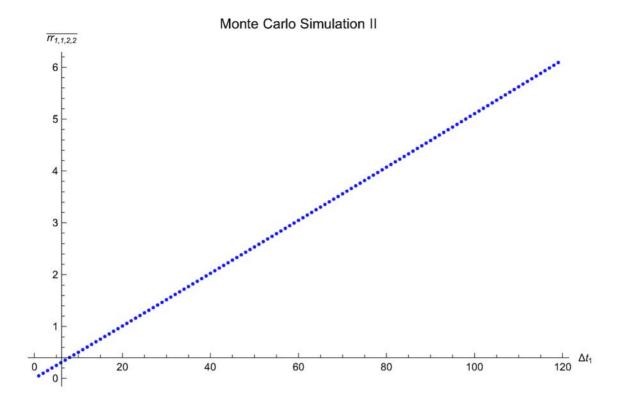


Figure 16. The mean residual risk and QC related cost versus the QC sampling time interval length of the Monte Carlo Simulation I. The mean residual risk measure  $\overline{rr_{1,1,2,2}}$  (upper plot) and the mean expected QC related cost measure  $\overline{ct_{1,1,2}}$  (lower plot) versus the length of the predefined QC sampling time intervals  $\Delta t_1$  of the Monte Carlo Simulation I. The means were estimated after 1000 single applications of the algorithm assuming random initial times  $t_0$ , with  $0 \le t_0 \le 1957.0$ . The x-axes origins are set to the mean length of the QC sampling time intervals  $\Delta t_i$  estimated to be optimal. The y-axes origins are set respectively to the mean residual risk measure  $\overline{rr_{1,1,2,2}}$  and the mean expected QC related cost measure  $\overline{ct_{1,1,2}}$  of the QC sampling time intervals estimated to be optimal.



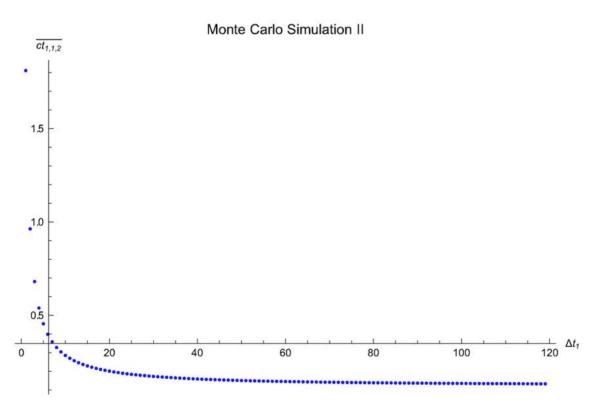
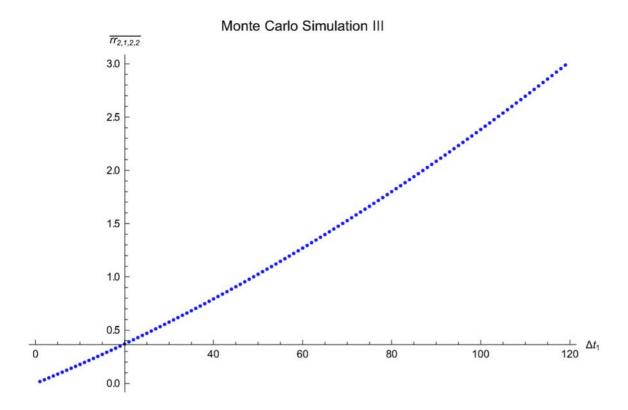


Figure 17. The mean residual risk and QC related cost versus the QC sampling time interval length of the Monte Carlo Simulation II. The mean residual risk measure  $\overline{rr_{1,1,2,2}}$  (upper plot) and the mean expected QC related cost measure  $\overline{ct_{1,1,2}}$  (lower plot) versus the length of the predefined QC sampling time intervals  $\Delta t_1$  of the Monte Carlo Simulation II. The means were estimated after 1000 single applications of the algorithm assuming random initial times  $t_0$ , with  $0 \le t_0 \le 13901.4$ . The x-axes origins are set to the mean length of the QC sampling time intervals  $\Delta t_i$  estimated to be optimal. The y-axes origins are set respectively to the mean residual risk measure  $\overline{rr_{1,1,2,2}}$  and the mean expected QC related cost measure  $\overline{ct_{1,1,2}}$  of the QC sampling time intervals estimated to be optimal.



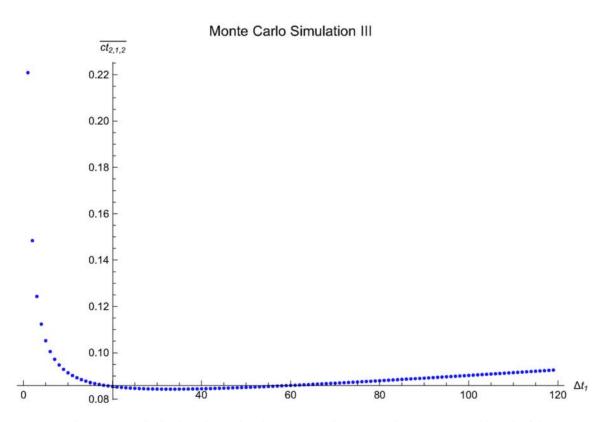


Figure 18. The mean residual risk and QC related cost versus the QC sampling time interval length of the Monte Carlo Simulation III. The mean residual risk measure  $\overline{rr_{2,1,2,2}}$  (upper plot) and the mean expected QC related cost measure  $\overline{ct_{2,1,2}}$  (lower plot) versus the length of the predefined QC sampling time intervals  $\Delta t_1$  of the of the Monte Carlo Simulation III. The means were estimated after 1000 single applications of the algorithm assuming random initial times  $t_0$ , with  $0 \le t_0 \le 1715.6$ . The x-axes origins are set to the mean length of the QC sampling time intervals  $\Delta t_i$  estimated to be optimal. The y-axes origins are set respectively to the mean residual risk measure  $\overline{rr_{1,1,2,2}}$  and the mean expected QC related cost measure  $\overline{ct_{1,1,2}}$  of the QC sampling time intervals estimated to be optimal.

dependencies between the critical-failure time probability density functions (see eqs (14) and (15)) as well as of the respective measurement error probability density functions (See Definition of functions assuming multivariate measurement error probability density functions in Appendix S1). Although the failure time probability density functions of some critical-failure modes of an analytical system may be independent, as for example the failure of an optical component of a photometric module and the purely mechanical failure of a sampling module, others will be dependent. There are techniques that can be used to estimate dependencies [19]. The parametric estimation of multivariate copulas is a method that could be applied [20]. If the dependencies cannot be estimated, then upper and lower bounds of the respective multiple failure time probability density functions can be estimated and interval analysis can be used. For example, we may have:

$$\mathbf{f}_{i,h}(t) = \left[ \mathbf{Min} \left( \mathbf{f}_i(t), \, \mathbf{f}_h(t) \right), \, \mathbf{Max} \left( \mathbf{f}_i(t), \, \mathbf{f}_h(t) \right) \right] \tag{67}$$

If the measurement error probability density functions are dependent then multivariate distributions could be used and the respective covariance matrices could be estimated (See *Definition of functions assuming multivariate measurement error probability density functions* in Appendix S1).

This is a large scale procedure that can be accomplished by the industry. Then a database could be established with the reliability analysis data that could be continuously updated with the failure data from the analytical systems in the field, operated by different operators, in different environments. Possibly a substantial commitment is required for such an effort to succeed, giving priority to the safety of the patient.

For the rigorous QC design and estimation of the optimal QC sampling time intervals it is necessary a risk analysis to be performed to correlate the size of the measurement error with the risk that can cause. Then the medically acceptable analytical error, the risk function that can be even a simple step function or a fuzzy function, and the acceptable risk and residual risk measures can be defined. The risk analysis is a very complex task too. It can be subjective or objective, quantitative or semi-quantitative and should be accomplished by the medical profession. In the future, as the potential of the data analysis will increase exponentially, appropriate risk functions should be estimated using evidence based methods.

The currently used QC design methods are based on an upper bound of the fraction of the measurements nonconforming to quality specifications [2–4]. I defined the decision levels of the applied QC rules using an approach that although is analogous to these methods, it is more clinically relevant as the risk measures based on the normalized sum of the 2<sup>nd</sup> upper and the absolute value of the 2<sup>nd</sup> lower partial moments of the measurement error with reference to *mte* and *-mte* respectively correlate better with the size of the critical error. In addition, I propose a mixture probability density function of the measurement error to model the "intermittent analytical error".

Preliminary results show that the algorithm I developed can be used to optimize in addition to the QC sampling time intervals the decision limits of the applied QC rules, given the residual risk and the acceptable risk rate  $RLr_d(S)$  (see eq.(36)). The optimization of both variables though is computationally intensive.

# References

 Department of Health and Human Services (2003) Medicare, Medicaid and CLIA Programs: Laboratory requirements relating to quality systems and certain personnel qualifications Federal Register. U.S. pp 3640–3714. There are numerous assumptions underlying the model I used:

- a. The critical-failure time probability density functions. I assumed general critical-failure time probability density functions to model a variable hazard rate with a bathtub curve. Any probability density function can be used including the exponential and the lognormal or any mixture distribution. If the failure time probability density functions cannot be estimated, then upper and lower bounds of them can be estimated and interval analysis can be used.
- b. The assumption of the independence of the failure modes. If the failure modes are dependent the respective dependence functions or at least upper and lower bounds of the respective multiple failure time probability density functions can be estimated.
- The assumption of the normality and additivity of the measurement error. Alternative assumptions can be used.
- d. The assumption of the same distribution of measurement error of the c levels of the controls. For a more general model a multivariate (c-variate) distribution of measurement error can be used (See Definition of functions assuming multivariate measurement error probability density functions in Appendix S1).
- e. The QC rules. I applied single value rules but alternative QC rules can be applied as well [16].
- f. The risk function is based on the normalized sum of the d<sup>th</sup> upper and the absolute value of the d<sup>th</sup> lower partial moments of the measurement error with reference to mte and -mte respectively. Simpler or more complex risk functions can be defined.
- g. The assumptions about the maintenance state. Alternative assumptions can be used as well.

# Conclusion

To optimize the QC planning process a reliability analysis of the analytical system and a risk analysis of the measurement error are needed. Then it is possible to rationally estimate the optimal QC sampling time intervals to sustain an acceptable residual risk with the minimum QC related cost.

# **Supporting Information**

## Appendix S1

Found at: doi:10.1371/journal.pone.0005770.s001 (0.18 MB DOC)

# **Acknowledgments**

I am grateful to Theofanis Chatzimichail and Dr. Katerina Chatzimichail, as well as to Gethsimani, Chrysavgi, Rallou, and Theodora, my family, for their continuing support and encouragement.

## **Author Contributions**

Conceived and designed the experiments: ATH. Performed the experiments: ATH. Analyzed the data: ATH. Contributed reagents/materials/analysis tools: ATH. Wrote the paper: ATH.

 Hatjimihail AT (1993) Genetic algorithms-based design and optimization of statistical quality- control procedures [published erratum appears in Clin Chem 1994 Feb;40(2):267]. Clin Chem 39: 1972–1978.



- Linnet K (1989) Choosing quality-control systems to detect maximum clinically allowable analytical errors. Clin Chem 35: 284–288.
- Westgard JO (1992) Charts of operational process specifications ("OPSpecs charts") for assessing the precision, accuracy, and quality control needed to satisfy proficiency testing performance criteria. Clin Chem 38: 1226–1233; discussion 1245–1250.
- Westgard JO, Oryall JJ, Koch DD (1990) Predicting effects of quality-control practices on the cost-effective operation of a stable, multitest analytical system. Clin Chem 36: 1760–1764.
- Parvin CA, Gronowski AM (1997) Effect of analytical run length on qualitycontrol (QC) performance and the QC planning process. Clin Chem 43: 2149–2154.
- Parvin CA, Robbins S 3rd (2007) Evaluation of the performance of randomized versus fixed time schedules for quality control procedures. Clin Chem 53: 575–580.
- Parvin CA (2008) Assessing the impact of the frequency of quality control testing on the quality of reported patient results. Clin Chem 54: 2049–2054.
- Duncan AJ (1956) The Economic Design of x Charts Used to Maintain Current Control of a Process. Journal of the American Statistical Association 51: 228–242.
- Banerjee PK, Rahim MA (1988) Economic design of x-control charts under Weibull shock models. Technometrics 30: 407–414.
- Linderman K, McKone-Sweet KE, Anderson JC (2005) An integrated systems approach to process control and maintenance. European Journal of Operational Research 164: 324–340.
- Panagiotidou S, Nenes G (2009) An economically designed, integrated quality and maintenance model using an adaptive Shewhart chart. Reliability Engineering & System Safety 94: 732–741.
- ISO (2007) Medical devices Application of risk management to medical devices. Geneva. pp 1–92.

- 14. Smith DJ (2001) Reliability, Maintainability and Risk. Oxford: Butterworth-Heinemann.
- Stamatelatos M, Vesely W, Dugan J, Fragola J, Minarick J, et al. (2002) Fault Tree Handbook with Aerospace Applications. Washington, DC: NASA. pp 1–205.
- Hatjimihail AT (1992) A tool for the design and evaluation of alternative qualitycontrol procedures [published erratum appears in Clin Chem 1992 Nov;38(11):2360] [see comments]. Clin Chem 38: 204–210.
- Dhilon BS (2000) Medical device reliability and associated areas. Boca Raton, Florida: CRC Press LLC. 240 p.
- Ferson S, Kreinovich V, Ginzburg L, Myers DS (2002) Constructing probability boxes and Dempster-Shafer structures. AlbuquerqueNew Mexico: Sandia National Laboratories, SAND2002-4015. pp 1–144.
- Ferson S, Nelsen RB, Hajagos J, Berleant DJ, Zhang J, et al. (2004) Dependence in probabilistic modeling, Dempster-Shafer theory, and probability bounds analysis. AlbuquerqueNew Mexico: Sandia National Laboratories, SAND2004-3072 SAND2004-3072. pp 1–141.
- Liebscher E (2008) Construction of asymmetric multivariate copulas. Journal of Multivariate Analysis 99: 2234–2250.
- Chen J, Bandoni A, Romagnoli JA (1997) Robust estimation of measurement error variance/covariance from process sampling data. Computers & Chemical Engineering 21: 593–600.
- Morad K, Y. Svrcek W, McKay I (1999) A robust direct approach for calculating measurement error covariance matrix. Computers & Chemical Engineering 23: 889–897.
- Leger MN, Vega-Montoto L, Wentzell PD (2005) Methods for systematic investigation of measurement error covariance matrices. Chemometrics and Intelligent Laboratory Systems 77: 181–205.