On-line estimation of the reaction rates from sampled measurements in bioreactors

I. Bouraoui *,** M. Farza * T. Menard * R. Ben Abdennour **
M. M’Saad *

* GREYC, UMR 6072 CNRS, Université de Caen, ENSICAEN,
6 Bd Maréchal Juin, 14050 Caen Cedex, FRANCE.
mondher.farza@unicaen.fr
** Unité de Recherche CONPRI, ENIG Gabès, Rue Omar Ibn El Khattab,
6029 Gabès, Tunisie

Abstract: Simple high gain observer-based estimators which allow the estimation of the reaction rates from the measurements of component concentrations inside bioreactors are presented. The main properties of these estimators lie in the fact that the measurements of the component concentrations are non available in a continuous manner, as generally assumed in most available algorithms, but only at sampling instants. The proposed estimators, called continuous-discrete observer, result from the design of available estimators which assume the availability of the measurements in a continuous manner. It is shown that for relatively small values for the sampling periods, which may be time-varying, the proposed continuous-discrete observers inherit the same performance as the purely continuous observers in terms of the accuracy of estimation and sensitivity to noise measurements. Simulations results dealing with typical bioreactor example are given in order to illustrate the performance and the main properties of the proposed estimators.

Keywords: High gain observer, Continuous-discrete time observer, Impulsive observer, Reaction rate, Bioreactor.

1. INTRODUCTION

The development of bioprocesses has been hampered by important obstacles. One of them is the lack of cheap and reliable instrumentation suited to real-time monitoring. In order to overcome this difficulty, theoretical frameworks have been developed to design ‘software sensors’ which are capable of coping with the lack of instrumental sensors. A software sensor is the association between a physical sensor (hardware) and an estimator or an observer (a software). The estimator or the observer is the software part which produces the on-line estimation of the state from the measurements supplied by the (physical) sensor. The use of software sensors for the estimation of the reaction rates inside bioreactors is of primary importance. This is because these rates are in general very complex functions of the operating conditions and the state of the process. The analytical modelling of these functions is often cumbersome and still constitutes the subject of continuing and intensive investigation Dochain (2008). Thus, their estimation saves bioengineers the trouble of choosing a particular model amongst the several ones described in the literature. Moreover, these estimates which are interesting for on-line control schemes, can also be used for basic investigations of the culture under consideration.

The use of state observers for on-line estimation of the reaction rates in bioreactors has been widely discussed in the literature (see for instance Bastin and Dochain (1990); Chen (1992); Farza and Chéruy (1994); Farza et al. (1997a, 1998, 1999); Zhang and Guay (2002); Dochain (2003); M´ ailleret et al. (2004); Moreno and Dochain (2008); Veloso et al. (2009); Chitralekha et al. (2010); Zarei and Poshtan (2010); Dabros et al. (2010); Battista et al. (2012); Zhu (2012); Bouraoui et al. (2015) and references therein). However, and even though issued from different approaches, the most available results deal with continuous-time measurements. It is worth mentioning that the digital implementation of these continuous-time observers is generally carried out without any redesign in the case where the sampling periods are small enough. On the contrary and for relatively high values for the sampling periods, the stability and the convergence properties of the sampled continuous-time observer may be lost and the look for other solutions becomes necessary. We can cite the solution such that the observer design is based on approximate discrete-time descriptions of the systems dynamics Bastin and Dochain (1990); Farza et al. (1998, 1997b). Such an approach does not allow to take into account the inter-sampled dynamics which is completely lost. Moreover, the underlying discrete-time representation may suffer from possible errors occurred in the sampling scheduling process. Such an issue has to be handled by appropriately redesigning the continuous time observer taking into account that the outputs measurements are available only at sampling instants. Indeed, in this paper, one shall focus on the design of continuous-discrete time observers which allows the on-line estimation of the reaction rates from the
measurements of some component concentrations which are only available at some sampling instants. The proposed observer is obtained from a redesigned version of a purely continuous-time one, namely an observer that assumes continuous-time measurements that has been proposed in Farza et al. (1997a, 1998, 2004). The obtained continuous-discrete time observer is firstly derived under an impulsive form: the corrective term depends on the difference between two constants that respectively correspond to the estimated and actual output values at the last sampling instant. It is time-varying and it particularly depends on the sampling periods. Of particular interest, it is then shown that the proposed impulsive observer can be written under the form of an hybrid system constituted by two subsystems: the first subsystem has the same structure as the purely continuous time observer where the non available outputs are replaced by appropriate predictions provided by the second subsystem.

The paper is organized as follows. In the next section, we recall bioprocess state space models which are the basis of reaction rates observers designs. The continuous-time observers of the reaction rates proposed in Farza et al. (1997a, 1998) and which will be subject of the redesign in order to account for the availability of the outputs measurements only at the sampling instants are also recalled. In section 3, the design of the impulsive continuous-discrete time observer are firstly derived and the main properties of the observer are emphasized and in particular compared to those of the purely continuous output observer. Then, one shows that the proposed impulsive observer can be written under the form of a hybrid system, allowing thereby to emphasize the relationship between this observer and the continuous output observer. Simulations results are given in section 4 in order to highlight the properties of the proposed observers. Finally, concluding remarks are given in section 5.

2. PROBLEM FORMULATION AND PRELIMINARY RESULTS

In this section, we first introduce the bioprocesses’ state space models which are used for the design of the reaction rates estimators. Then, the continuous time output observers which provide on-line estimates for the reaction rates are briefly recalled.

2.1 Modelling of bioprocesses

A biotechnological process can be defined as a set of $N$ components, called state variables, which interact through $M$ biochemical reactions, $r_1, \ldots, r_M$. These, in general, take place in a stirred tank bioreactor. The dynamical balance model that should be considered is the following Ordinary Differential Equation (ODE):

$$\dot{x} = Yr(\xi, t) - D\xi + F - G$$

where the vectors $\xi, F, G \in \mathbb{R}^N$ denote the component concentrations (state variables), the mass feed rates, and the mass outflow rates in gaseous form, respectively; $Y$ is the yield coefficients matrix with $N$ rows and $M$ columns, $r \in \mathbb{R}^N$ is the vector of the reaction rates and $D \in \mathbb{R}^{N \times N}$ is the dilution rate matrix. Generally, the number of reaction rates is lower than or equal to the number of the components i.e. $M \leq N$. Moreover, the yield coefficients matrix is usually of full rank. Indeed, we shall assume in the sequel that $M \leq N$ and $Y$ is of full rank column i.e. $Y$ is assumed to be left invertible. We also assume that all the state variables, $\xi_1, \ldots, \xi_N$ are measured.

Before recalling the equations of the continuous-time output observers, which allows the estimation of the reaction rates from the continuous-time measurements of the component concentrations, we adopt as in Bastin and Dochain (1990); Farza et al. (1998); Dochain (2003) the following unifying (but not simplifying) stance for modelling the reaction rates based on the following fact: a reaction can take place only if all the reactants are present in the reactor. Otherwise said, the reaction rate is necessarily zero whenever the concentration of one of the reactants (including autocatalysts) is zero. Thus, the vector of reaction rates $r(\xi, t)$ can be factored as follows:

$$r(\xi, t) = H(\xi)\alpha(\xi, t)$$

where $H$ is a $M \times M$ diagonal matrix whose the $j^{th}$ diagonal term correspond to the product of the reactants involved in the $j^{th}$ corresponding reaction; The term $\alpha(\xi, t) = [\alpha_1(\xi, t), \ldots, \alpha_M(\xi, t)]^T$ is a vector of time-varying parameters and each $\alpha_j(\xi, t)$ is called the specific reaction rate since it is the reaction rate per unit of each reactant. Notice that since the diagonal terms of the matrix $H$ correspond to the reactants of the reactions, these terms can be assumed to be bounded away from zero along the fermentation and the matrix $H(\xi)$ is invertible. Indeed, we shall assume in the sequel that this matrix is indeed invertible.

2.2 Estimation of the reaction rates from continuous measurements

The design of an observer for the estimation of the (specific) reaction rates from the component concentrations which are assumed to be available in a continuous manner has been made under the assumption that the first time derivatives of the specific reaction rates are bounded Farza et al. (1998) i.e.

$$\exists \delta > 0; \forall t \geq 0, \dot{\alpha}(t, \xi) \leq \delta$$

Thus, the mathematical balance model that should be used for the observer design can be written as follows:

$$\begin{align*}
\dot{\xi}(t) &= YH(\xi(t))\alpha(t) - D(t)\xi(t) + F(t) - G(t) \\
\dot{\alpha}(t) &= \varepsilon(t)
\end{align*}$$

where $\varepsilon(t)$ is an unknown and bounded function. The observer equations can be written as follows Farza et al. (1998); Bourouli et al. (2015):

$$\begin{align*}
\dot{\hat{\xi}}(t) &= YH(\hat{\xi}(t))\hat{\alpha}(t) - D(t)\hat{\xi}(t) + F(t) - G(t) \\
\dot{\hat{\alpha}}(t) &= -\theta H(\hat{\xi}(t))\hat{\alpha}(t) - \xi(t)
\end{align*}$$

where $\xi$ and $\hat{\alpha}$ denote the estimates of $\xi$ and $\alpha$, respectively, $K_1$ and $K_2$ are $N \times N$ matrices and they have to be chosen such that the block matrix $\begin{pmatrix} -K_1 & I_N \\ -K_2 & 0 \end{pmatrix}$ is Hurwitz; finally $\theta > 0$ is a scalar design parameter. The observer equations can be written in a condensed form. Indeed, set

$$\begin{align*}
x &= \begin{pmatrix} \xi \\ \hat{\alpha} \end{pmatrix}, & \dot{x} &= \begin{pmatrix} \dot{\xi} \\ \dot{\hat{\alpha}} \end{pmatrix}, & A(x) &= \begin{pmatrix} 0 & YH(\xi) \\ 0 & 0 \end{pmatrix}, \\
D &= \begin{pmatrix} D \\ 0 \end{pmatrix}, & F &= \begin{pmatrix} F \\ 0 \end{pmatrix}, & G &= \begin{pmatrix} G \\ 0 \end{pmatrix}, & K &= \begin{pmatrix} K_1 \\ K_2 \end{pmatrix}, \\
\Delta_\theta &= \text{diag}(\theta I_N, \theta^2 I_N), & \Lambda(\hat{\xi}) &= \text{diag}(I_N, YH(\hat{\xi}))
\end{align*}$$
Using these notations, observer (5) can be rewritten as follows:

\[ \dot{\hat{x}} = A(\hat{\xi})\hat{x} - \bar{D}\hat{x} + \bar{F} - \bar{G} - \Lambda(\hat{\xi})\Delta K(\hat{\xi} - \xi) \]  

(6)

For clarity purposes, we shall introduce the following variables:

\[ z = \begin{bmatrix} \hat{x} \\ \hat{\xi} \end{bmatrix} = \begin{bmatrix} z_1 \\ z_2 \end{bmatrix} = H(\xi, \alpha) \]  

and \( \hat{z} = \begin{bmatrix} \hat{x} \\ \hat{\xi} \end{bmatrix} = \begin{bmatrix} \dot{z}_1 \\ \dot{z}_2 \end{bmatrix} = H(\hat{\xi}, \hat{\alpha}) \). Notice that the variable \( z \) (resp. \( \hat{z} \)) can be deduced from \( x \) and \( \alpha \) (resp. \( \hat{x} \) and \( \hat{\alpha} \)) from the following invertible relation \( z = \Lambda(\xi)x \) (resp. \( \hat{z} = \Lambda(\hat{\xi})x \)). The main properties of observer (5) are summarized in the following theorem:

**Theorem 1.** Consider system (4) subject to assumption (3) together with observer (5). Then, \( \forall \theta > 0 \):

\[ \|\hat{z}(t) - z(t)\| \leq \sigma \|\tilde{z}(0) - z(0)\| + \frac{\sigma\delta}{\mu\theta} \]  

where \( \sigma, \mu > 0 \) are positive real and \( \delta \) is the upper bound of \( \bar{z}(z) \).

Notice that in the case where the \( \varepsilon = 0 \) i.e. the reaction rates are constant, the observation error converges exponentially to zero. In the case where \( \delta \neq 0 \), the estimation error can be made as small as desired by choosing values of \( \varepsilon \) sufficiently high. However, such values may render more sensitive the observer with respect to the unavoidable noise measurements. Hence, the choice of \( \varepsilon \) is a compromise between satisfactory tracking of the reaction rates variations and a good dealing of the proposed observer with respect to the output noise measurements. It should be emphasized that since the variables \( \hat{z} \) and \( \hat{x} \) (resp. \( z \) and \( x \)) are correlated through the invertible relation \( \hat{z} = \Lambda(\hat{\xi})\hat{x} \) (resp. \( z = \Lambda(\xi)x \)), then the estimation error \( \hat{x} - x \) satisfies the same properties as \( \hat{z} - z \).

### 3. ESTIMATION OF THE REACTION RATES FROM SAMPLED MEASUREMENTS

We now assume that the measurements of the component concentrations are not available in a continuous manner but only at the sampling instants that satisfy \( 0 \leq t_k < t_{k+1} < \ldots < t_k < t_{k+1} < \ldots \) with time-varying sampling intervals \( \tau_k = t_{k+1} - t_k \) and \( \lim_{k \to \infty} \tau_k = +\infty \). One naturally assumes that the time intervals \( \tau_k \)'s are bounded away from zero by \( \tau_m \) and upperly bounded by the upper bound of sampling partition diameter \( \tau_M \) i.e.

\[ 0 < \tau_m \leq \tau_k \leq \tau_M, \quad \forall k \geq 0 \]  

(7)

#### 3.1 The impulsive continuous-discrete time observer design

We shall first introduce the proposed observer under an impulsive form. Then, an equivalent output predictor of this observer shall be given. The continuous-discrete time impulsive observer that allows the on-line estimation of the reaction rates from the measured samples of the component concentrations can be written as follows:

\[
\begin{aligned}
\dot{\hat{z}}(t) &= YH(\hat{\xi}(t))\dot{\hat{\xi}}(t) - D(t)\hat{\xi}(t) + F(t) - G(t) - \theta K_1e^{-\theta K_1(t-t_k)}(\hat{\xi}(t_k) - \xi(t_k)) \\
\dot{\hat{\xi}}(t) &= -\theta K_1e^{-\theta K_1(t-t_k)}(\hat{\xi}(t_k) - \xi(t_k)) + K_2e^{-\theta K_2(t-t_k)}(\hat{\xi}(t_k) - \xi(t_k))
\end{aligned}
\]  

(8)

Notice that the equations of the continuous-discrete time impulsive observer (8) are very similar to those of the outputs continuous observer (5). Indeed, the unique difference in these equations lies in the correction term: the time-continuous term \( (\xi(t) - \hat{\xi}(t)) \) in the outputs continuous observer is replaced by the time-discontinuous term \( e^{-\theta K_1(t-t_k)}(\hat{\xi}(t_k) - \xi(t_k)) \) which is updated at each sampling instant \( t_k \). This issue shall be detailed later.

Before giving the main properties of the continuous-discrete time observer (8), we shall rewrite it in a condensed form using the notation introduced above. Indeed, the impulsive observer (8) can be rewritten as follows:

\[ \dot{\hat{z}} = A(\hat{\xi})\hat{x} - \bar{D}\hat{x} + \bar{F} - \bar{G} - \Lambda(\hat{\xi})\Delta K(\hat{\xi} - \xi) \]  

(6)

The main properties of the observer (9), explained in the \( z \) coordinates introduced above, are summarized in the following theorem.

**Theorem 2.** Consider system (4) subject to assumption (3) together with observer (8). Then, \( \forall \theta > 0 \); there exist positive constants \( \eta_0 > 0 \); \( \eta_0(\tau_M) = \mu_0 \theta(1 - \frac{\tau_k}{\tau_M})e^{-\mu_0(\tau_M)} > 0 \) such that if the upper bound of the sampling partition diameter \( \tau_M \) is chosen such that \( \tau_M < \tau_0 \), then for every \( \hat{z}(0) \in \mathbb{R}^{2N} \), we have:

\[ \|\hat{z}(t) - z(t)\| \leq \sigma \|\tilde{z}(0) - z(0)\| + \frac{\sigma\delta}{\mu\theta} \]  

where \( \tau_m, \tau_M \) are respectively the lower and upper bounds of the sampling partition diameter as given by (7), \( \sigma > 0 \) is the positive real given by theorem 1 and \( \delta \) is the upper bound of \( \bar{z}(z) \).

Notice that, as in the continuous output case, the estimation error converges exponentially to zero in the case where the reaction rates are constant. Otherwise, this error is ultimately bounded. We shall put forward the relationship between the rate of the exponential decreasing to zero and the ultimate bound of the estimation error in the continuous output case and the case where the outputs are available only at sampling instants. To this end, we shall consider the case where the sampling period is constant, namely \( \tau_M = \tau_m = T_s \). Indeed, in such a case and according to the expression of \( \eta_0(T_s) \) given in Theorem 2, one has:

\[ \lim_{T_s \to 0} \eta_0(T_s) = \lim_{T_s \to 0} \mu_0 \theta \left( \frac{T_s}{T_s} - 1 \right) e^{-\mu_0 T_s} = \mu_0 \theta \]  

(10)

and one recover the same exponential decay rate as in the continuous output case. Let us now focus on the ultimate bound of the asymptotic estimation error which specifies as follows:

\[ \sigma \theta T_s \frac{2 - e^{-\eta_0(T_s)T_s}}{1 - e^{-\eta_0(T_s)T_s}} \]  

One has:

\[ \lim_{T_s \to 0} T_s \frac{2 - e^{-\eta_0(T_s)T_s}}{1 - e^{-\eta_0(T_s)T_s}} = \lim_{T_s \to 0} \left( T_s + \frac{T_s}{1 - e^{-\eta_0(T_s)T_s}} \right) = \lim_{T_s \to 0} \frac{1}{\eta_0(T_s)} = \frac{1}{\mu_0 \theta} \]

Hence, one meets when the sampling period goes to the zero, the same ultimate as in the continuous output case, i.e. \( \frac{1}{\mu_0 \theta} \). We now show that the above impulsive continuous-discrete time observer can be written under an output predictor form: i.e. a form similar to the output continuous observer (5) but where the output \( \xi(t) \) which is
available only at the sampling instances is replaced by an appropriate prediction issued from an ordinary differential equation which is reinitialized at each sampling instant with the just available output.

3.2 Output predictor form of the impulsive observer

The impulsive observer can be written under the following output predictor form Bouraoui et al. (2015):

$$\begin{align*}
\dot{x} &= A(\xi)x - \hat{D}x + \hat{F} - \hat{G} - \Delta^+ (\xi)\Delta_0 K(\dot{\xi} - \zeta) \\
\dot{\xi} &= YH(\xi)x - \hat{D}\dot{\xi} + F - G \text{ for } t \in [t_k, t_{k+1}]
\end{align*}$$

(11)

The first equation of system (11) is very similar to the continuous output observer (6) with the sole difference that the measured output $\xi(t)$ in the case of the continuous observer is replaced by $\zeta(t)$. In fact, the variable $\zeta$ is a prediction of the output $\xi$ which is not available between two sampling instant. The prediction $\zeta$ is the solution of the second ODE in system (11). The structure of this ODE is very similar to that of the balance equation satisfied by the output $\dot{\xi}$ in system (4). This ODE is resolved between each two successive sampling instants $t_k$ and $t_{k+1}$ and the initial value is equal to the value of the output at the instant $t_k$. Let us now show that the form (11) is indeed equivalent to the impulsive form (9). Indeed, let $\Omega(t) = \dot{\xi}(t) - \zeta(t)$ be the error between the output estimate and its prediction provided by (11). From (11), one gets:

$$\Omega(t) = -\theta K(\dot{\xi}(t) - \zeta(t))$$

and accordingly an observer of the form (9).

Notice that the gain of the observer (9) is chosen as $K_1 = 2I_2$ and $K_2 = I_2$ in such a way that the block matrix $\begin{pmatrix} -K_1 & 0 \\ 0 & K_2 \end{pmatrix}$ has all its poles located at $(-1)$. For simulation purposes and in order to generate the pseudo-measurements of $X$ and $P$, we have chosen the following expressions for the reaction rates Farza et al. (1998):

$$\begin{align*}
\dot{X}(t) &= \frac{\mu_{max}SX}{(K_S + S + \frac{S_0}{\tau})} - \frac{K_P}{(K_P + P)}X(t) \\
\dot{P}(t) &= \frac{\nu_{max}SX}{K_S + S} - \frac{K_P}{(K_P + P)}P(t)
\end{align*}$$

(16)

where $\mu_{max}$, $\nu_{max}$, $K_S$, $K_S$, $K_I$, $P_I$ and $K_P$ are constant kinetic parameters. The simulation experiments have been performed using the following initial conditions:

$$\begin{align*}
X(0) &= 2.6 \text{ g.l}^{-1}, & P(0) &= 0 \text{ g.l}^{-1} \\
S(0) &= 79.6 \text{ g.l}^{-1}, & r_1(0) &= r_2(0) = 0 \text{ g.l.h}^{-1}
\end{align*}$$

The values of the kinetic parameters are:

$$\begin{align*}
\mu_{max} &= 0.3 \text{ h}^{-1}, & \nu_{max} &= 0.11 \text{ h}^{-1}, & k_1 &= 5.1g.g^{-1} \\
k_2 &= 1.5 \text{ g.g}^{-1}, & K_S &= 0.26 \text{ g.l}^{-1}, & K_S &= 9.5 \text{ g.l}^{-1} \\
K_P &= 8g.l^{-1}, & K_I &= 297 \text{ (g.l)}^{-2}, & P_I &= 85 \text{ g.l}^{-1} \\
S_n &= 95 \text{ g.l}^{-1}
\end{align*}$$

The dilution rate varies as a trapezoidal signal from 0.1 to 0.2 l.h$^{-1}$ as shown in figure 1. In order to simulate practical situations, all the simulation experiments have been carried out with noisy data measurements: the measurements of $X$ and $P$ issued from the simulation of system (13)-(16) are corrupted by an additive gaussian
noise with zero mean value and a variance equal to 0.05. The simulation studies have been performed as follows. First, several simulation experiments have been carried out assuming continuous time output measurements. This allows to obtain a lower bound on the design parameter \( \theta \) for which the underlying continuous time observer performs well i.e. a good compromise between an admissible tracking of the kinetic parameter variation and a good behavior of the observer with respect to noise measurements. The value of \( \theta \) ensuring such a compromise was about 1.5. Then, an other set of simulation experiments has been performed with this fixed design parameter value (\( \theta = 1.5 \)) and different values for the sampling period. From an experiment to the other, the value of the sampling period was constant, \( \tau_M = T_s \), and has been increased until reaching the maximum allowable value \( \tau_M \) for which the performance of the continuous-discrete time observer still be quite satisfactory. The obtained value was \( \tau_M = 3h \).

We have reproduced in figures 3 and 4 four sets of results corresponding to the estimation of the reaction rates \( r_1 \) and \( r_2 \) obtained with the same value of the design parameter \( \theta = 1.5 \). The first set provides the estimates of \( r_1 \) and \( r_2 \) in the case of continuous time measurements (figures 3) and they are obtained by simulating an observer of the form (5). These estimates can serve as a reference (the ideal case) for the estimates obtained with the continuous-discrete time observer (15). The second, third and fourth sets are given in figure 4 and they are obtained with \( T_s = 0.1h, T_s = 1h, \) and \( T_s = 3h \), respectively. As expected, the best estimates are obtained with smaller values of the sampling period. Moreover, for relatively low values of \( T_s \) (e.g. \( T_s = 0.1h \)), the obtained estimates are quite similar to those obtained with continuous measurements.

We do recall that the expressions of the reaction rates, introduced for simulation purposes and in order to obtain the pseudo-measurements of \( X \) and \( P \), are not known by observer (14).

5. CONCLUSIONS

Simple high gain observer-based estimators have been proposed in order to on-line estimate the reaction rates in bioreactors. The measurements of the component concentrations used by the estimators in order to provide the reaction rates estimates, are available at sampling instant only and consequently there is an incentive for such estimators. The proposed estimators are issued from the redesign of purely continuous-estimators, that is estimators which assume that the measurements of the component concentrations are available in a continuous manner. It has been shown that the proposed estimators keep the main characteristics of the continuous ones: their design does not assume or require any specific relationships between the component concentrations and the reaction rates. Furthermore, their tuning is achieved through the calibration of a single design parameter.

We have shown through simulation that for relatively small but realistic values of the sampling periods, the proposed estimators inherit the main properties and performance of the continuous ones: they are capable to accurately estimate the reaction rates when these parameters are subject to significant variations and when the available measurements are corrupted by noise. The obtained results are encouraging to use the proposed estimators for control objective and in particular in adaptive control schemes.

![Fig. 1. Time evolution of the dilution rate](image1)

![Fig. 2. Continuous noisy measurements of X and P](image2)

![Fig. 3. Estimation of \( r_1 \) and \( r_2 \) from continuous noisy measurements](image3)

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Fig. 4. Estimation of $r_1$ and $r_2$ from sampled noisy measurements.