**Microbiological Process Discussion**

**Principles in the Design of Continuous Sterilizers**

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 Properly designed continuous sterilization offers a method for overcoming undesirable destruction of nutritive quality and formation of toxic substances in fermentation media, two consequences often associated with batch sterilization. Also, operation of a pure culture fermentation process on a continuous basis requires a continuous supply of sterilized medium. Although this medium can be sterilized batchwise intermittently in alternate tanks in quantities large enough to permit an uninterrupted supply, the ideal method from an operational viewpoint is continuous sterilization. Because it often results in process improvement and operational advantages, continuous sterilization is finding increased interest in the fermentation industry.

A number of different types of continuous sterilizers have been described in the literature. From a sterilization point of view they differ mainly in their heating and cooling characteristics. From an operational viewpoint, they differ in their control stability, ease of manipulation, and operational maintainability. Each type is used, of course, where its particular advantages are most suitable. The purpose of this paper is to review the various types of continuous sterilizers, and, based on their temperature characteristics, to illustrate the use of recently developed analytical design methods for calculating the time needed to achieve the sterilization requirement dictated by a process.

**Continuous Sterilizers Used in Fermentation Processes**

Although continuous sterilization has been mentioned in connection with fermentation processes in a number of review articles in such a way that one implies it is the chief method of sterilization in the industry, not many direct references to its use in specific fermentation processes are available. Some actual applications for 12 different processes, cited in the literature, are summarized in table 1. Included in this summary are brief descriptions of the types of sterilizers employed in each application.

**Types of Sterilizers and Their Characteristics**

A continuous sterilizer consists of three main sections. They are (a) a heating section, (b) a holding section, and (c) a cooling section. Sterilizers can be classified by the mode of flow of nutrient medium and the manner of heat transfer in each section. All of the sterilizers described in table 1 reduce to at least one of each of the three main sections illustrated in figure 1.

Stirred-tank heating and holding sections shall not be considered in the ensuing discussion since very long retention times are required in these units to achieve reasonable degrees of sterilization. Stirred-tank heating

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sections, operating at steady-state, are essentially instantaneous heaters and holding sections combined.

From a sterilization viewpoint, the primary differences among the other types of sections shown in figure 1 are the temperature characteristics in an element of fluid flowing through them. Figure 2 illustrates the temperature-time profile of an element of medium in each of the heating and cooling sections under consideration. The holding sections usually operate adiabatically, or nearly enough so, to be treated as isothermal units. Where energy losses are noticeable, a linear temperature-time profile may be assumed.

An optimal sterilization results when peak sterilization temperature is attained with minimal time exposure. In this respect, the steam injector heater is best because final temperature depends only upon material and enthalpy balances, and not at all upon rate phenomena. Next in order of preference is the plate exchanger. The plate exchanger heats medium more rapidly than the spiral or tubular exchanger because of the greater heat transfer area per unit of flowing medium and higher heat transfer coefficient due to induced turbulence.

Regarding the cooling sections, the stirred-tank, or quench cooler with adequate heat removal capacity, is distinctly the best single cooler because hot medium is instantly cooled to sublethal temperatures by dilution in the colder medium. The water injector and flash coolers, in that order, are the next best. In a flash chamber, internal pressure in the process system prevents (from a sound pure culture basis) cooling below about 220 F. A water injector can cool to below this

### TABLE 1

<table>
<thead>
<tr>
<th>Process</th>
<th>Sterilizer Sections</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baeicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,3-Butanediol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butanol, acetone, ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium 2-ketogluconate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanoocobalamin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal amylase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itaconic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium gluconate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Various types of continuous sterilizer sections

**Figure 2.** Temperature-time profiles in various heating and cooling sections.
temperature, but alone could not achieve process temperature without excessive medium dilution. A combination of these latter two methods with each other, or with any other cooling section, will generally be required. The plate exchanger is better than the spiral or tubular exchanger, and the immersed coil because of the same reasons cited for exchanger heating sections.

For the special case of countercurrent exchangers where the hot and cold streams have equal flow rates and heat capacities, the heating and cooling curves reduce to straight-line curves. These are not illustrated in figure 2. They do occur frequently, however, in heat recovery sections where hot medium is cooled by cold raw medium.

**Design Principles**

Methods for calculating heat sterilization times have been described by Deindoerfer and Humphrey (1957, 1959). (See Deindoerfer and Humphrey, 1959, for definitions of symbols employed.) The design criterion for a sterilization is related to the reduction in bacterial count from its initial level to some selected final level depending upon the degree of confidence one wishes to place on the sterilization. The design criterion was expressed as

\[ \nabla = \ln \frac{N_t}{N_0} = \int_0^t k \, dt \]  

(1)

The design criterion, \( \nabla \), is then a measure of the amount of bacteria to be destroyed and its value is characteristic of the size of the sterilization. Since \( k \) may be related to temperature by an Arrhenius type relationship \( (k = Be^{-a/R}T) \), equation 1 may be written as

\[ \nabla = B \int_0^t e^{-a/R}dT \]  

(2)

The integration of equation 2 is accomplished by substituting for temperature its functional relationship with time. These relationships for continuous sterilizers appear in table 2. For adiabatic holding sections, integration of equation 2 is straightforward. The solution appears as equation 7 in table 3. The integrations for the other temperature-time profiles listed in table 2 have been presented by Deindoerfer and Humphrey (1959). These solutions also appear in table 3. The solutions involve exponential integrals of the first or second order, values of which are easily obtained from tables, or for large arguments, from simple computation. The constants in the integrated equations combine into a number of dimensionless parameters. They are determined from the thermal-death characteristics of the design organism and the operating characteristics of the sterilizer.

**TABLE 2**

*Temperature-time relationships in exchanger heating and cooling sections*

<table>
<thead>
<tr>
<th>Exchanger Operation</th>
<th>Temperature-Time Profile</th>
<th>( b )</th>
<th>( K )</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heating using isothermal heat source</td>
<td>( T_{c1} = T_H(1 - be^{-kt}) )</td>
<td>( T_H - T_{c1} )</td>
<td>( UA )</td>
<td>3</td>
</tr>
<tr>
<td>Heating using countercurrent heat source of equal flow rate and heat capacity</td>
<td>( T_H = T_{c1}(1 + bKt) )</td>
<td>( \Delta T )</td>
<td>( UA )</td>
<td>4</td>
</tr>
<tr>
<td>Cooling using isothermal heat sink</td>
<td>( T_{H1} = T_C(1 - be^{-kt}) )</td>
<td>( T_C - T_{H1} )</td>
<td>( UA )</td>
<td>5</td>
</tr>
<tr>
<td>Cooling using countercurrent heat sink of equal flow rate and heat capacity</td>
<td>( T_{H1} = T_H(1 + bKt) )</td>
<td>( -\Delta T )</td>
<td>( UA )</td>
<td>6</td>
</tr>
</tbody>
</table>

**TABLE 3**

*Design equations for continuous sterilizers*

<table>
<thead>
<tr>
<th>Type of Section</th>
<th>Design Equation</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heating or cooling using isothermal heat source or sink</td>
<td>( \nabla = \frac{B}{K} \left[ E_1 \left( \frac{a}{1 - b} \right) - E_1 \left( \frac{a}{1 - be^{-kt}} \right) \right] - \frac{Be^{-a}}{K} \left[ E_1 \left( \frac{a}{1 - b} - a \right) - E_1 \left( \frac{a}{1 - be^{-kt} - a} \right) \right] )</td>
<td>7</td>
</tr>
<tr>
<td>Heating or cooling using countercurrent heat source or sink of equal flow rate and heat capacity</td>
<td>( \nabla = \frac{Ba}{bK} \left[ E_1 \left( \frac{a}{1 + bKt} \right) - E_2(a) \right] )</td>
<td>8</td>
</tr>
<tr>
<td>Adiabatic holding</td>
<td>( \nabla = Be^{-a}t )</td>
<td>9</td>
</tr>
</tbody>
</table>
APPLICATION OF DESIGN EQUATIONS

The use of the design equations in table 3 will be illustrated in a typical but hypothetical sterilization carried out in each of two types of sterilizers described in the literature. For sake of illustration, assume the following sterilization requirements:

Rate of sterile medium supply to fermentors: 1000 gal/hr
Design duration: 3 months
Raw medium bacterial population: $20 \times 10^6$ cells/gal
Raw medium temperature: 75°F
Sterile medium temperature: 85°F

Assuming that the total bacterial population is comprised of the most heat resistant spore species (this has the effect of introducing a safety factor), the design criterion is then

$$\nabla = \ln \frac{N_0}{N} = \ln \frac{(20 \times 10^6 \text{cells/gal})(1 \times 10^3 \text{gal/hr})}{(24 \text{hr/day})(90 \text{days})} = 38.3$$

Also, assume that the most heat resistant spores in the medium are characterized by an activation energy for thermal death of 67,700 cal/gmol and a constant, $B$, in the Arrhenius equation, of $1 \times 10^{10.2} \text{sec}^{-1}$.

Steam injector-flash cooler sterilizer. The first type of sterilizer under consideration, described by Wheat (1953), employs instantaneous heating and cooling sections. The sterilizer is illustrated in figure 3. Notice that the hot medium is vacuum flashed. This admittedly is poor practice for strict pure culture fermentations. It is used in this illustration as a matter of convenience.

Steam at 100 psig is available to bring the sterilizer to a dependable operating temperature of 290°F. The problem is to determine the time required in the holding section to achieve the desired sterilization.

Solution. Because heating and cooling are accomplished almost instantaneously, the design equation for an adiabatic holding section (equation 9) is all that is required.

$$\nabla = Be^{-at}$$

The value of $a$ can be calculated at a medium temperature of 290°F, or 750°F.

$$a = \frac{\mu}{RT}$$

$$a = \frac{(67,700 \text{cal/gmol})}{(1.10 \text{cal/gmol} \times 0°F)(750°F)} = 82.1$$

Rearrangement of equation 7, and substitution of the known factors, yields a sterilization time as follows:

$$t = \frac{(38.3)}{(1 \times 10^{10.2} \text{sec}^{-1})(e^{-82.1})} = 12.2 \text{sec}$$

Thus by heating the medium to 290°F and holding at this temperature for 12.2 sec the desired sterilization is accomplished.

**Exchanger-type sterilizer.** A more complex type of sterilizer to consider is one described by Whitmarsh (1954), consisting of three plate-exchanger sections and a holding tank. For this illustration the holding tank is replaced by a tubular holding section. The sterilizer is shown in figure 4, along with the operating temperatures of the unit. The cooling section is actually two sections, one for heat recovery and one for final heat removal. The over-all heat transfer coefficients and transfer areas for each section are as described below. Observing that the medium remains 15 sec in each section, the problem is to calculate: first, the amount of sterilization accomplished in the heating and cooling sections; and, second, the time required in the holding section to assure achievement of the desired sterilization.

Solution. The initial heating occurs in a countercurrent (equal flow rates) section. The final heating is accomplished in a section with condensing steam as an isothermal heat source. Cooling is carried out in countercurrent sections with equal flow rates of each stream.

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**Figure 3.** Steam injector-flash cooler continuous sterilizer (after Wheat, 1953).

**Figure 4.** Plate exchanger continuous sterilizer (after Whitmarsh, 1954).
Then
\[ \nabla_{\text{holding section}} = \nabla_{\text{total}} - (\nabla_{\text{heating sections}} + \nabla_{\text{cooling sections}}) \]

Consider first the final heating section, a case of an isothermal heat source. Equation 7 is applicable.

\[ \nabla = \frac{B}{K} \left[ E_1 \left( \frac{a}{1 - b} \right) - E_1 \left( \frac{a}{1 - e^{-Kt}} \right) \right] \]

The dimensionless parameters \( B/K \), \( be^{-a} / K \), \( a \), \( b \), and \( bKt \); and the integrands of the exponential arguments \( a/(1 - b) \), \( a/(1 - b) - a \), \( a/(1 - be^{-Kt}) \), and \( a/(1 - be^{-Kt}) - a \) need to be evaluated in order to solve for \( \nabla \). This requires that the various factors involved in these groups first be determined.

**Determination of factors.** The following information is known:

- \( t = 15 \text{ sec} \)
- \( U = 785 \text{ BTU/hr} \times \text{ft}^2 \times ^\circ F \)
- \( A = 25 \text{ ft}^2 \)
- \( w = 2.32 \text{ lb/sec} \)
- \( c = 1 \text{ BTU/lb} \times ^\circ F \)
- \( T_H = 298 ^\circ F = 758 ^\circ R \)
- \( T_{c1} = 225 ^\circ F = 685 ^\circ R \)
- \( T_{c2} = 290 ^\circ F = 750 ^\circ R \)
- \( \mu = 67,700 \text{ cal/gmol} \)
- \( B = 1 \times 10^{36.2} \text{ sec}^{-1} \)

The time constant, \( K \), is calculated as follows:

\[ K = \frac{UA}{Wc} \]

Where \( W \) is the mass of medium in contact with the exchanger surface area, \( A \), then

\[ W = wt \]

or

\[ W = (2.32 \text{ lb/sec})(15 \text{ sec}) = 34.8 \text{ lb} \]

and

\[ K = \frac{(785 \text{ BTU/hr} \times \text{ft}^2 \times ^\circ F)(25 \text{ ft}^2)}{(34.8 \text{ lb})(1 \text{ BTU/lb} \times ^\circ F)} \]

\[ = 564 \text{ hr}^{-1} = 0.157 \text{ sec}^{-1} \]

**Determination of exponential integral arguments:**

\[ a = \frac{\mu}{RT_H} \]

\[ a = \frac{(67,700 \text{ cal/gmol})}{(1.10 \text{ cal/gmol} \times ^\circ R)(758 ^\circ R)} = 81.2 \]

\[ b = \frac{T_H - T_{c1}}{T_H} \]

\[ b = \frac{758 ^\circ R - 685 ^\circ R}{758 ^\circ R} = 0.0963 \]

\[ be^{-a} = 0.0963 e^{-(0.157 \text{ sec}^{-1})(15 \text{ sec})} = 0.00913 \]

\[ \frac{B}{K} = 1 \times 10^{36.2} \text{ sec}^{-1} \]

\[ = 6.37 \times 10^{36.2} \]

\[ \frac{Be^{-a}}{K} = 6.37 \times 10^{36.2} e^{-81.2} = 40.2 \]

**Evaluation of exponential integral functions:**

\[ E_1(89.9) = e^{-89.9} \approx 1.12 \times 10^{-41} \]

\[ E_1(81.9) = e^{-81.9} \approx 3.08 \times 10^{-88} \]

\[ E_1(8.67) = 1.78 \times 10^{-5} \]

\[ E_1(0.74) = 0.347 \]

**Calculation of \( \nabla \):**

\[ \nabla = \frac{Ba}{bK} \left[ E_2 \left( \frac{a}{1 + bKt} \right) E_3(a) \right] \]

To arrive at a value for \( \nabla \) for this section, the dimensionless parameters, \( Ba/bK \) and \( bKt \), and the integrands of the second-order exponential integral arguments \( a \) and \( a/(1 + bKt) \) must be determined. This requires prior knowledge of the various factors in these groups.
Determination of factors. The following information is known:

\[ t = 15 \text{ sec} \]
\[ U = 375 \text{ BTU/hr} \times \text{ft}^2 \times \degree \text{F} \]
\[ A = 25 \text{ ft}^2 \]
\[ W = 34.8 \text{ lb} \]
\[ C = 1.0 \text{ BTU/lb} \times \degree \text{F} \]
\[ T_{c_1} = 75 \text{ F} = 535 \degree \text{R} \]
\[ T_{c_2} = 225 \text{ F} = 685 \degree \text{R} \]
\[ T_{h_1} = 290 \text{ F} = 750 \degree \text{R} \]
\[ T_{h_2} = 140 \text{ F} = 600 \degree \text{R} \]
\[ \mu = 67,700 \text{ cal/gmol} \]
\[ B = 1 \times 10^{38.2} \text{ sec}^{-1} \]

The time constant, \( K \), is evaluated as previously.

\[ K = 270 \text{ hr}^{-1} = 0.075 \text{ sec}^{-1} \]

Determination of dimensionless parameters:

\[ a = \frac{\mu}{RT_n} \]
\[ b = \frac{-\Delta T}{T_n} \]
\[ Ba = \frac{(1 \times 10^{38.2} \text{ sec}^{-1})(82.1)}{750 \degree \text{R}} = -1.266 \times 10^{36.2} \]
\[ bKt = (-0.0866)(0.075 \text{ sec}^{-1})(15 \text{ sec}) = -0.0976 \]

Determination of exponential integral arguments:

\[ a = 82.1 \]
\[ \frac{a}{1 + bKt} = \frac{82.1}{1 - 0.0976} = 89.1 \]

Evaluation of exponential integral functions:

\[ E_2(82.1) = \frac{e^{-82.1}}{(82.1)^2} = 2.94 \times 10^{-46} \]
\[ E_2(89.1) = \frac{e^{-89.1}}{(89.1)^2} = 2.00 \times 10^{-42} \]

Calculation of \( \nabla \):

\[ \nabla = -1.095 \times 10^{30} \left[ (2.00 \times 10^{-42}) - (2.94 \times 10^{-46}) \right] = 5.1 \]

Similar calculations on the other heating and cooling sections also yield \( \nabla \) values, but, because of the lower temperatures involved in these sections, they do not contribute significantly to the sterilization, that is, their \( \nabla \) values are much less than 1.

Thus, the remaining sterilization to be accomplished in the holding section at 290 F can be calculated.

\[ \nabla_{\text{holding section}} = 38.3 - (14.5 + 5.1) = 18.7 \]

The operating sections therefore contribute more than 50 per cent of the sterilization in the heating and cooling of the medium. The holding time needed to complete the sterilization is calculated from equation 2. The specific reaction rate at 290 F is 3.15 sec\(^{-1}\).

\[ t = \frac{18.7}{3.15 \text{ sec}^{-1}} = 5.9 \text{ sec} \]

Thus, because the medium is heated and cooled over a finite time interval, the holding time at peak sterilization temperature is considerably reduced from the time required if the medium were heated and cooled instantaneously, as in the first example.

Acknowledgments

The authors appreciate the helpful information supplied by American Heat Reclaiming Corporation and the DeLaval Separator Company concerning heat transfer performance characteristics of plate heat exchangers.

Summary

The examples cited illustrate the use of certain design equations for calculating the amount of sterilization accomplished in various sections of typical sterilizers described in the literature. These design equations offer an improved method for evaluating and predicting continuous sterilizer performance in a rational manner.

Comparison of the two examples used points out that, when heating and cooling portions of the sterilization cycle require finite time periods, their contribution to the sterilization operation can be appreciable.

References


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