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THE CONCEPTUAL DESIGN OF A PERFUSION REACTOR USING A COMPLEXITY MEASURE

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ABSTRACT

The conceptual design of a perfusion reactor is the subject of this paper. The main objective of the reactor is the provision of nutrients to living cells grown in a porous medium fabricated of a given ceramic foam. In order to increase reactor throughput, the nutrients should be provided in a minimum time, without affecting the cell life. Various layouts of identical ceramic-foam pieces hosting the cells are proposed, the purpose being to select the variant with the highest likelihood of optimum performance, in the absence of a detailed mathematical model. A simple model is proposed, drawn from the discipline of hydraulic dynamical systems, which leads to a flow-complexity measure. The variant with the lowest complexity is then selected, for which a possible embodiment is proposed.

INTRODUCTION

Design researchers have devised models of the design process with the purpose of understanding the process and finding means to best implementing it when facing one particular design job. The three most frequently cited models are those due to French [1], the VDI, the acronym of *Verein Deutscher Ingenieure* (Association of German Engineers) [2] and Pahl and Beitz [3]. In all these models we can identify four main steps: analysis of the problem; conceptual design; embodiment design; and detailed design. We focus here on the second step, which comprises, in turn, two tasks, (*i*) generation of variants and (*ii*) production of a short list of the variants with the highest likelihood of meeting *optimally* all specifications, *functional requirements* and *desired features*—“wishes” in [3]. Task (*i*), falling in the realm of creative thinking, lies beyond the scope of the paper, our focus being the second task. To this end, we resort to the concept of *complexity* in the realm of design.

The concept of complexity is quite broad, with a rich literature on the subject being available. The most abstract and general notion of the concept known to the authors is that proposed mainly by Kolmogorov and Chaitin in the fifties and the sixties, and fully developed by Li and Vitány [4]. However, due to the generality of the foregoing concept, its application to specific fields has remained quite elusive. We will not pursue in this paper the application of this concept, but rather use an alternative approach. A comprehensive literature survey on the concept of complexity in general, and more specifically in the context of product design and its documentation, is available in [5].

The use of complexity as a means to assess the performance of a design solution is not new. Attempts to use complexity in this context have been proposed by ElMaraghy and Urbanic [6], who applied the concept to the closely related field of manufacturing engineering, and by Suh [7], who tied the concept to his *Axiomatic Design* formalism. More recently, Khan et al. [8] proposed a framework to assess design variants in the context of the

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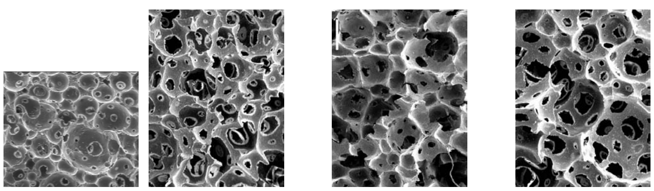
conceptual design of robots. Here we resort to this framework to propose a measure of *flow-complexity* in the design of a *perfusion reactor*. This paper should show that the same framework can be applied to design jobs in a variety of disciplines.

THE TUB PERFUSION REACTOR

The design project that motivated this study consists in the application of a novel ceramic foam produced from the aluminum-oxide powder AKP 50, as supplied by Japan's Sumitomo Chemical Corp. Ltd. The ceramic foam was developed at the Technical University of Berlin (TUB) Institut für Werkstoffwissenschaften und -technologien. This foam is produced out of a ceramic powder mixed with modified beef serum albumina (BSA) and foamed in a field of electromagnetic waves before sintering. Thus, a stiff open porous ceramic structure is generated with an average pore size of 0.15 mm [9]. A sample of four different types of foam is displayed in the microphotographs of Fig. 1.



(a) (b) (c) (d)

Figure 1. Various foam types obtained from various protein-derivatives: (a) simple BSA; (b) maltose-enriched BSA; (c) acetyl-enriched BSA; and (d) glucose-enriched BSA

The application envisioned is the culture of human cells for the production of organs to replace their sick counterparts. A key process in the culture is the provision of nutrients to the cells. As the cells cannot withstand high pressure levels, and the nutrients should traverse the ceramic medium in the shortest time, so as to maximize reactor throughput, a rough model of the nutrient flow is needed, as outlined in the balance of this section.

A Rough Model

The phenomena of nutrient flow through the foam ceramic is rather complex, to be analyzed using models of *fluid-flow through porous media*—a thorough study with a rich bibliography on the subject is available in [10]. The mathematical model pertinent to such phenomena is an initial-boundary-value problem (IBVP) in a system of diffusion nonlinear partial differential equations, under given initial and boundary conditions. At the conceptual stage, however, the constructive details of the ceramic medium are not yet determined. Indeed, the structure of the porous medium depends on many factors, first and foremost the specific type of cells being processed. In order to simplify the discussion, we shall assume that the ceramic pieces are cylindrical, of height h and radius r.

The design problem at hand is defined below:

Determine the optimum layout of a set of pieces of ceramic foam, of given dimensions, that will lead to a minimum nurturing time.

With the information available, a highly realistic mathematical model is out of the question. We will pursue instead a *rough, approximate model* of the phenomena, under plausible assumptions. These assumptions are justified on the simplest possible model applicable to the phenomenon under modeling. Such a simple model is lumped—as opposed to distributed—and exhibits both resistive and capacitive behaviors. Moreover, based on the fixed dimensions of the ceramic-foam pieces, the capacity of these is negligible when compared with that of the reservoir holding the nutrient. The latter is assumed to be a homogeneous Newtonian fluid, whose viscosity is taken into account by the linear resistor of the model. To be true, not all assumptions below are independent; they are listed nevertheless, while pointing out their interdependence, to ease their understanding. The assumptions are

(*i*) The medium is approximated as a lumped hydraulic resistor of resistance R, in series with a lumped hydraulic capacitor of capacitance C;
(*ii*) the capacitance of the ceramic foam is negligible when compared with that of the reservoir providing the nutrient;
(*iii*) the nutrient, which flows across the resistor, behaves as an incompressible, linearly viscous fluid, its viscosity being accounted for by means of the resistor;
(*iv*) the pressure drop Δp across the resistor is proportional to the rate of nutrient flow q—a consequence of assumption (*iii*)—the proportionality constant being the resistance, namely, $\Delta p = Rq$;
(*v*) while the reactor equivalent resistance changes according to reactor-design layout, the hydraulic capacitance is the same for all layouts, a consequence of assumption (*ii*).

The simple hydraulic model adopted here is depicted in Fig. 2, in which: p_a denotes the atmospheric pressure; ρ_n the nutrient density; g the gravity acceleration; R the hydraulic resitance; and y the hydraulic head of the nutrient. In the model we assume that no pressure source is available other than the atmospheric pressure, as cell-life support precludes the use of a compressor. Furthermore, resistance and capacitance are intertwined in the ceramic foam, with a rather complex distribution that can be analyzed only by means of a stochastic model. In

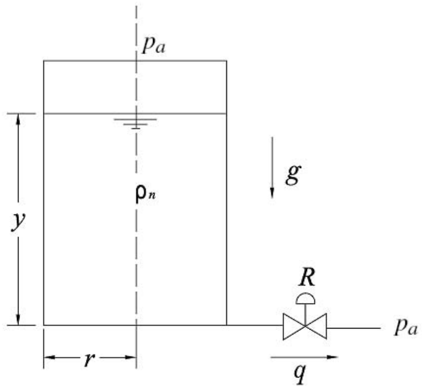


Figure 2. The hydraulic model of the nutrient flowing through the ceramic medium

our rough model, we assume that the resistance is confined to the resistor R and the capacitance to the capacitor C.

By hypothesis, the pressure drop across the resistor is Rq; the pressure at the left of the resistor is $p_a + \rho_n gy$; that to the right of the resistor is p_a; the nutrient flow q equals the rate at which the volume of the reservoir of Fig. 2 is decreasing, namely, $-A_r\dot{y}$, where A_r is the area of the cylindrical reservoir. Upon equating the pressure drop $\Delta p = p_a + \rho_n gy - p_a$ with $-RA_r\dot{y}$ we obtain the well-known linear model $\rho_n gy = -RA_r\dot{y}$, whence an initial-value problem is derived, namely,

$$\dot{y} = -\frac{\rho_n g}{RA_r} y, \quad y(0) = y_0 \tag{1}$$

Further, the coefficient of y—not including the negative sign—can be cast in the form

$$\frac{\rho_n g}{RA_r} \equiv \frac{1}{RA_r/(\rho_n g)} \equiv \frac{1}{RC_r}, \quad C_r \equiv \frac{A_r}{\rho_n g} \tag{2}$$

where C_r is known as the *hydraulic capacitance* of the model reservoir at hand. Moreover, because the product RC_r has units of time, it is usually represented as τ, and termed the *time constant* of the model, which now can be cast in the simpler form

$$\dot{y} = -\frac{1}{\tau} y, \quad y(0) = y_0 \tag{3}$$

The time response of the initial-value problem (3) is known to be

$$y(t) = y_0 e^{-t/\tau} \tag{4}$$

its time-derivative being $\dot{y} = -(y_0/\tau)e^{-t/\tau}$, whence, $\dot{y}(0) = -y_0/\tau$. It is now apparent that the flow rate $q = -A_r\dot{y} = A_r y_0 e^{-t/\tau}/\tau$ (a) decays exponentially with time and (b) attains its maximum value at time $t = 0$, this maximum being directly proportional to $A_r y_0$—and hence, to the reservoir capacitance C_r—and inversely proportional to the time constant. Hence, in order to speed up the flow of the nutrient through the ceramic medium, the time constant should be made as small as possible. Now, as the time constant is the product RC_r, and the capacity has been assumed to be constant for all layouts, the flow rate will be maximized upon minimizing the equivalent resistance of the reactor. Therefore, our goal henceforth is to find the layout variant with the minimum resistance. Our evaluation scheme can thus be made based on the resistance alone. However, resistance is a dimensional quantity, with units of pressure divided by units of flow rate, i.e.,

$$[R] = \frac{\text{N}}{\text{m}^2}\frac{\text{s}}{\text{m}^3} = \frac{\text{Ns}}{\text{m}^5} = \frac{\text{kg}}{\text{m}^4\text{s}} \tag{5}$$

Hence, any performance evaluation based on hydraulic resistance alone cannot be integrated into other performance measures of the reactor under other criteria, as stated above. Hence, we shall resort to a flow-complexity measure that is both monotonically decreasing with resistance and non-dimensional.

LAYOUT VARIANTS

The simplest model of a hydraulic resistance consists of a prismatic porous medium, of height h and constant cross section of area A. The *resistivity* ρ of the medium is a material property, independent of the geometry. The resistance of such a medium is given by

$$R = \rho\frac{h}{A} \tag{6}$$

For example, if the resistor has a cylindrical geometry, of height h and radius r, as shown in Fig. 3(a), its resistance, which we shall label R_{axial} to emphasize that the flow takes place along the axis of the cylinder, becomes $R_{\text{axial}} = \rho\frac{h}{\pi r^2}$.

In the foregoing model we have assumed that the area traversed normally by the flow is constant. The same model can also be applied to other cases. For example, if the resistance is a hollow circular cylinder of height h, inner wall of radius r_i and outer wall of radius r_o, then we can divide the resistance into a series of small, hollow, coaxial cylinders of internal and external radii r and $r + \mathrm{d}r$, respectively; then, the flow can be thought of as traversing at right angles a resistor of "length" $\mathrm{d}r$ and cross-sectional area $2\pi hr$—see Fig. 3b. Thus, the differential resistance dR of this thin-walled cylindrical resistor is

$$\mathrm{d}R = \rho \frac{\mathrm{d}r}{2\pi h r} \tag{7}$$

The total resistance for this case, that we shall label R_{rad}, to emphasize that the flow in question is radial, can then be found by integration of the foregoing expression, thereby obtaining

$$R_{\text{rad}} = \int_{r_i}^{r_o} \rho \frac{\mathrm{d}r}{2\pi h r} \equiv \frac{\rho}{2\pi h} \int_{r_i}^{r_o} \frac{\mathrm{d}r/r_o}{r/r_o}$$

Hence,

$$R_{\text{rad}} = \frac{\rho}{2\pi h} \ln\left(\frac{r_o}{r_i}\right) \tag{8}$$

Therefore, $\lim_{r_i \to 0} R_{\text{rad}} \to \infty$, which makes sense, as, when the internal radius r_i vanishes, the flow is prevented from occurring, and hence, $q = 0$, regardless of the pressure difference across the resistor.

Resistors can be laid out in either series or parallel arrays. The series and parallel arrays of axial resistors are obvious. Series arrays of radial resistors can be implemented by means of a concentric layout, exactly in the same way as the resistance of a thick-walled hollow cylindrical resistor was calculated, namely, as an array of infinitely many coaxial arrays of thin-walled radial resistors of height h, radius r and thickness dr. Parallel arrays of the same resistors can be implemented by stacking individual radial resistors, not necessarily identical, with their axes coincident. For completeness, we illustrate in Fig. 4 a serial and a parallel array of axial resistors, while in Fig. 5 we illustrate the same arrays of radial resistors.

We thus have two basically different types of resistors, axial and radial; each type can be laid out in either series or parallel arrays. Moreover, axial and radial resistors can also be combined in either series or parallel arrays. The various possible combinations can thus be laid down according to six basic variants, namely,

1. Axial-series;
2. axial-parallel;
3. radial-series;
4. radial-parallel;
5. series combination of axial and radial; and
6. parallel combination of axial and radial.

Of course, axial and parallel arrays can themselves be laid out in either series or parallel arrays, to form, for example, a parallel array of series arrays. The number of variants is thus unlimited. For the sake of conciseness, we will limit ourselves to the above six basic variants, which are henceforth referred to as $V_1, V_2, \ldots, V_6$.

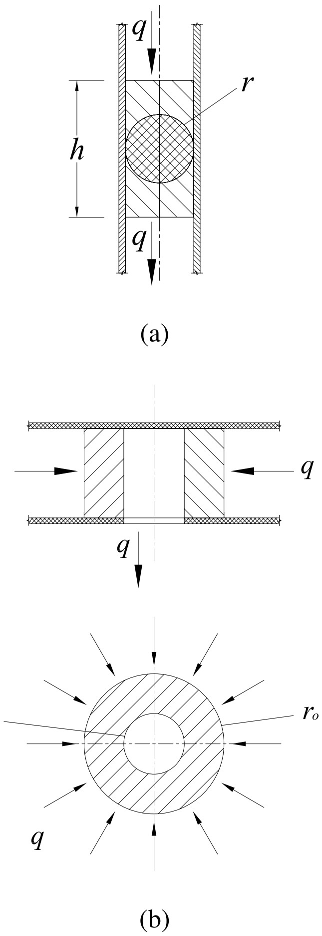
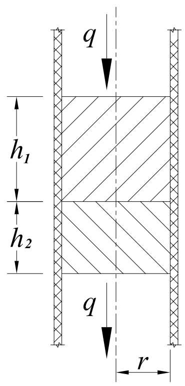


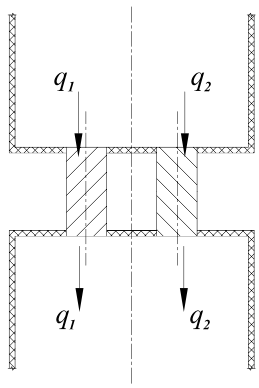
Figure 3. Axial and radial flows across a hydraulic resistor

VARIANT ASSESSMENT

In order to assess the suitability of the variants for the function at hand we need a performance measure that is (*i*) applicable to all possible variants and (*ii*) amenable to integration into a more general design framework that includes other factors such as fabrication and production costs. The latter calls for a *non-dimensional* performance measure. In this regard, *complexity* seems appropriate, as this concept is both quite general and non-dimensional. Indeed, complexity is an attribute of virtually any concept, and hence, allows the comparison of quite disparate items, that otherwise would be impossible to compare. For example, a grain of rice and a human being are quite disparate, yet both have a *genome* and the genome of each has a complexity associated with it, its length. We will thus adopt *flow-complexity* as a performance measure, and tie this with the resistance R_v of a given variant v. As well, we assume that, to be fair, all variants comprise the same number of identical ceramic-foam cylinders. In following the concepts proposed by Khan et al. (2007), we



(a)



(b)

Figure 4. Axial resistors in: (a) a series array; and (b) a parallel array

define the flow-complexity K as

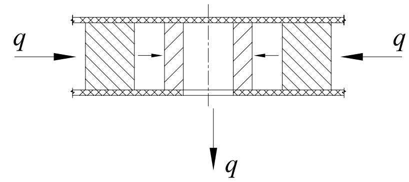
$$K = 1 - e^{-R_v/R_0} \tag{9}$$

where R_0 is a *reference resistance*. For concreteness, we define R_0 as the resistance of the ceramic medium under axial flow, i.e.,

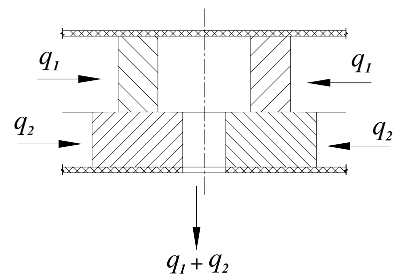
$$R_0 = \rho\frac{h}{A} \tag{10}$$

From its definition, K lies between 0 and unity. The absence of a resistor, $R = 0$, leads to a value of $K = 0$, while an infinite resistance leads to $K = 1$.

In the assessment process, we shall consider only ceramic-foam pieces of one single shape and dimensions, as stated at the outset. Moreover, regarding variants $V_1, \ldots, V_4$, we shall assume n pieces in the array, and recall that the equivalent resistance R_s of a series array of n identical resistors R_0 is nR_0; likewise, the equivalent resistance R_p of a parallel array of the same is



(a)



(b)

Figure 5. Radial resistors in: (a) a series array; and (b) a parallel array

obtained as the reciprocal of the equivalent *admittance*—the reciprocal of the resistance—of the array, which is additive, and hence, $R_p = R_0/n$.

Furthermore, regarding the radial resistor, we cannot assign a value to the ratio r_o/r_i because this will depend on the ratio of the volume of voids to that of the dimensions of the cylindrical piece, but the volume of voids is dependent on the type of cell and the time elapsed since the cell was inserted till the moment in which it is nourished—cells grow by self-division. In the absence of such a value, we shall assume that r_o is *at least* twice as big as r_i. To make further calculations simple, we assume that $r_o = er_i \approx 2.71828185r_i$, and hence, $\ln(r_o/r_i) = 1$ in eq.(8), whence, $R_{\text{rad}} = \rho/(2\pi h)$.

The complexity of each of the first four variants is thus

$$K_1 = 1 - e^{-nR_0/R_0} = 1 - e^{-n} \tag{11}$$

$$K_2 = 1 - e^{-R_0/(nR_0)} = 1 - e^{-1/n} \tag{12}$$

$$K_3 = 1 - e^{-nr^2/(2h^2)} \tag{13}$$

$$K_4 = 1 - e^{-r^2/(2nh^2)} \tag{14}$$

From the above expressions it is apparent that $K_2 < K_1$ and $K_4 < K_3$, but it is not possible to tell the relation between K_2 and K_4,

Figure 6. A sample of a piece of ceramic foam with $h = 10$ mm and $r = 5$ mm

as the r/h ratio is variable. The dimensions with which current cylindrical samples are produced are $h = 10$ mm and $r = 5$ mm, as shown in Fig. 6, and hence, $r^2/(2h^2) = 0.125 < 1$, the conclusion being that $K_4 < K_2$, and hence, of all first four variants, the radial-parallel layout is the least complex, and hence, the best. To be true, some larger samples have also been produced, with $h = 10$ mm and $r = 15$ mm, for which $r^2/(2h^2) = 1.125 > 1$ and, hence, the axial-parallel array becomes better than its radial-parallel counterpart. However, as we shall see below, V_6 beats both V_2 and V_4.

In order to assess the two remaining variants, we assume a series and a parallel array of an axial and a radial resistor, thereby leading to two resistance values, R_s and R_p, respectively. The implementation of these arrays is shown in Figs. 7(a) and (b). Actually, the layout of Fig. 7(a) is a series of two reservoirs, each with its own capacitor: the first capacitor is the one providing the radial flow into the radial resistor; the second is that of the small reservoir enclosed by the inner walls of the radial resistor. Given the relative sizes of the two capacitors, the second is considered to be negligible, thereby obtaining a series array of a radial and an axial resistor.

The equivalent resistance values R_s and R_p are

$$R_s = R_0 + R_{\rm rad} = \rho\frac{2h^2 + r^2}{2\pi h r^2} \tag{15}$$

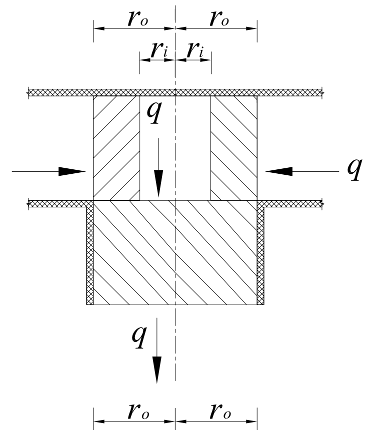
$$R_p = \frac{R_0 R_{\rm rad}}{R_0 + R_{\rm rad}} = \rho\frac{h}{\pi(2h^2 + r^2)} \tag{16}$$

the corresponding complexity values being

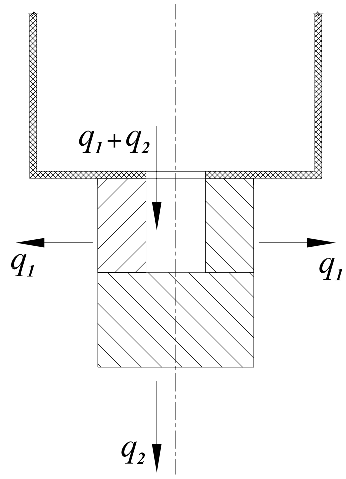
$$K_5 = 1 - e^{-R_s/R_0} = 1 - e^{-(2h^2+r^2)/(2h^2)} \tag{17}$$

$$K_6 = 1 - e^{-R_s/R_0} = 1 - e^{-r^2/(2h^2+r^2)} \tag{18}$$

whence, apparently, $K_6 < K_5$ for any value of the ratio r/h. Moreover, upon comparison of K_4, with $n = 2$ for a fair comparison, with K_6, it is apparent that $K_6 < K_4$, provided that $r^2/(2h^2) < 1$.



(a)



(b)

Figure 7. Radial and axial resistors combined in: (a) a series array; and (b) a parallel array

However, if $r^2/(2h^2) > 1$, as is the case for the larger samples, then $K_4 < K_6$. Nevertheless, V_6 need not be implemented as a stand-alone variant; it can be implemented in a parallel array. If we use, for example, two identical V_6 layouts in parallel, we will obtain a complexity K_{6p} that turns out to be better than K_2 with $n = 2$, namely,

$$K_{6p} = 1 - e^{-r^2/2(2h^2+r^2)} = 1 - e^{-1/[2+(2h/r)^2]}$$

which is apparently smaller than $1 - e^{-1/2} = K_2$ for $n = 2$. As a consequence, the parallel radial-axial array is the best of all six variants, unless, of course, a large-enough number n of resistors in series are used. The downside of a large n is, apparently, the space that such an array would take. By the same token, an equal number of V_6 arrays can be used in parallel, thereby defeating, in terms of flow-complexity, whatever number of parallel radial resistors is used.

The outstanding question is how to implement V_6, as the layout depicted in Fig. 7(b) is only a sketch. A large-enough area of ceramic piece has to be fastened to the reservoir, which calls for a realistic embodiment. This can be achieved as depicted in Fig. 8a. In this simple layout, a stepped cylindrical shape is proposed, so as to provide for a fastening area and a support to take the pressure on the influx side. A drawback of this embodiment is the corner, which is likely to house impurities and is difficult to clean properly. As an alternative, a departure from the cylindrical shape is proposed, as depicted in Fig. 8b. In this case, a fastening area and a support for the pressure on the influx side are provided by a portion of the surface of the frusto-conical ceramic piece.

The optimum layout has similarities with nature. Indeed, it functions as the mammary glands of mammals.

Overall Design Complexity

Flow-complexity is only one of multiple complexity criteria arising in the overall design job. Other criteria to consider, although left outside of this paper, are manufacturability, production cost, maintenance, etc. In general, we will end up with N independent complexity criteria $K_1, K_2, \ldots, K_N$—not to be confused with the variant complexities defined above—one of which is flow-complexity, and all lying between 0 and unity. Flow-complexity can be readily integrated into the overall design complexity K by means of a *convex combination* of partial complexities, namely,

$$K = \sum_{1}^{N} w_i K_i, \quad 0 \leq w_i \leq 1 \tag{19}$$

which thus guarantees that the overall complexity K also lies between 0 and unity. Of course, weights w_i are to be selected in terms of the relative relevance of each criterion. The latter can be established using, for example, the evaluation and selection methods described in [1], [2] and [3].

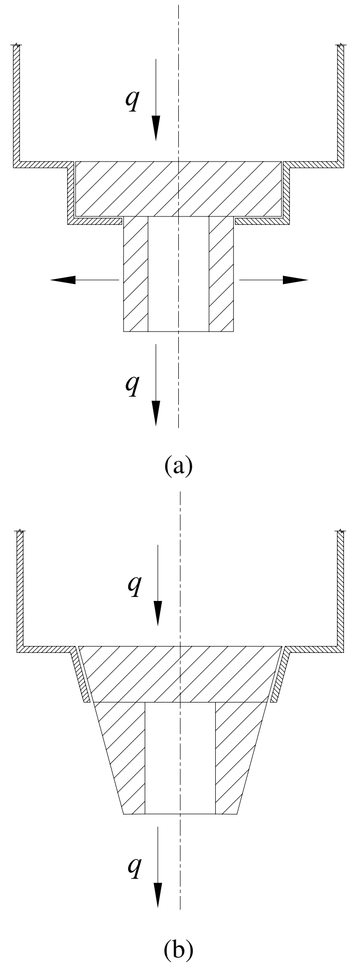


Figure 8. Embodiment possibilities of the radial-axial parallel array: (a) a simple layout; and (b) an improved version of (a)

EPILOGUE

The use of non-dimensional performance functions in design is standard practice. Non-dimensional quantities allow a comparison among all of them, as they do not have physical units attached to them. For the purposes of this paper, it should be clear that a dimensionless group, in the sense of *dimensional analysis*, of quantities is not needed. Moreover, the relation of eq.(9) is intended to produce a complexity measure K bounded between 0 and unity. This relation thus maps the ratio R_v/R_0 nonlinearly from the unbounded domain $[0, \infty[$ into a bounded domain. A linear map would not have been able to do the same. Using a similar mapping, any other performance quantity, like R_v/R_0, can be mapped into the same bounded domain [0, 1], to produce a set of complexity measures $\{K_i\}_1^N$, all of them a) lying within the same bounded domain and b) bearing a monotonic relation with a given unbounded performance quantity. All such complexity measures are then integrated into one single complexity measure, lying in the same bounded domain, by means of the convex combination (19).

Furthermore, as stated in the paper upfront, a host of issues around the comprehensive design of the perfusion reactor have not been considered in this paper. Indeed, cost, manufacturability, maintainability, reliability, and so on have not been integrated into one single complexity measure, but this is doable, once suitable complexity measures are defined for all the items at stake. For the integration of various complexity measures into a single one, the reader is referred to [8].

Finally, the concept of complexity, as proposed here, is quite different from the concept by the same name that is propounded by Suh [7]. As a matter of fact, the authors never intended to suggest that Suh's complexity is the most appropriate definition for application in design. This is a highly debatable issue, in which we never intended to be involved within the scope of this paper.

CONCLUSIONS

The motivation of this paper is the TUB Perfusion Reactor, currently under development at Technische Universität Berlin. While one prototype has been produced, with cylindrical pieces of ceramic, further development is still underway. As a means to assist the designer, a rough hydraulic model of the ceramic pieces was proposed as a means to evaluate six basic variants of ceramic-foam layouts. The purpose of the work reported here is to find the optimum layout of the ceramic pieces that will be able to supply nutrients to the cells in a minimum time, with the purpose of maximizing reactor throughput. At the outset, we considered only cylindrical shapes of the ceramic pieces. In the course of this work, and attending practical considerations, a shape that departs from the current one came up naturally, namely, frusto-conical. The evaluation of the six layouts was made possible by resorting to the model here proposed. Upon tying this model with the concept of complexity, the integration of flow-complexity with other criteria such as cost, manufacturability and maintenability will be possible. The next prototype is to be provided with frusto-conic pieces, which are currently under fabrication.

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[1] Besides the third co-author, Profs. H. Schubert, R. King, and L. Kroh, all of the TU Berlin, are collaborating in this project.

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