CFD simulation of an internal spin-filter: evidence of lateral migration and exchange flow through the mesh

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Abstract In the present work Computational Fluid Dynamics (CFD) was used to study the flow field and particle dynamics in an internal spin-filter (SF) bioreactor system. Evidence of a radial exchange flow through the filter mesh was detected, with a magnitude up to 130-fold higher than the perfusion flow, thus significantly contributing to radial drag. The exchange flow magnitude was significantly influenced by the filter rotation rate, but not by the perfusion flow, within the ranges evaluated. Previous reports had only given indirect evidences of this exchange flow phenomenon in spin-filters, but the current simulations were able to quantify and explain it. Flow pattern inside the spin-filter bioreactor resembled a typical Taylor-Couette flow, with vortices being formed in the annular gap and eventually penetrating the internal volume of the filter,

thus being the probable reason for the significant exchange flow observed. The simulations also showed that cells become depleted in the vicinity of the mesh due to lateral particle migration. Cell concentration near the filter was approximately 50% of the bulk concentration, explaining why cell separation achieved in SFs is not solely due to size exclusion. The results presented indicate the power of CFD techniques to study and better understand spin-filter systems, aiming at the establishment of effective design, operation and scale-up criteria.

Keywords Animal cell perfusion culture · Cell retention device · Computational fluid dynamics (CFD) · Fluid exchange · Lateral migration · Spin-filter

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Introduction

Spin-filters (SF) have been proposed as cell retention devices for animal cell culture several decades ago (Himmelfarb et al. 1969) and became a popular device for perfusion cultivations both for small-scale studies and large-scale processes (Castilho and Medronho 2002; Chu and Robinson 2001; Figueredo et al. 2005). They can be either placed inside the bioreactor (internal spin-filters) or in an external recirculation loop. When placed externally to the bioreactor, they are also known as vortex-flow filters (Castilho and Medronho 2002, 2008).

In spite of the many published reports employing spin-filters, the principles governing cell separation in these devices are not fully understood so far (Vallez-Cheteanu 2006). The complexity of the fluid and particle dynamics around the SF and the turbulent character of the flow rules out the possibility of obtaining analytical solutions for the equations describing the flow field and cell trajectories, hampering the understanding of its operation principles and the proposal of suitable criteria for SF design and operation.

Several works have dealt with the understanding of this device. Favre and Thaler (1992) proposed that high rotation rates providing fluid removal forces (calculated as the shear stress at the mesh surface times the projected cell surface area) in the order of 10^{-11} N would be enough to prevent colonization of the mesh surface by cells. However, Deo et al. (1996) have shown that cells growing in suspension, like NS0 cells, actually clog SFs even at fairly large rotation speeds. Yabannavar et al. (1992) and later Vallez-Cheteanu (2006) proposed the hydrodynamic lift to be crucial regarding the probability of a cell to hit and eventually clog the filter mesh. Vallez-Cheteanu (2006) also stated that the centrifugal acceleration was of relevance regarding filter clogging and could be adopted as a criterion for scale-up. Keeping the centrifugal acceleration constant would allow achieving similar cell retentions at larger scales. Vallez-Cheteanu et al. (2007) showed that, at low centrifugal accelerations, the longevity of spin-filters with relatively small mesh size decreased when the perfusion rate was increased, whereas increasing either centrifugal acceleration or mesh size reduced the fouling incidence. They also found that by using ultrasonic technology to promote filter vibration induced by a piezo actuator, they could reduce filter fouling, doubling the operation time before clogging.

For spin-filter scale-up, Yabannavar et al. (1994) proposed as scale-up criterion an expression for the ratio between drag and lift force. This criterion proved to be effective for bioreactor volumes in the range of 12–175 L. These researchers had also observed in a previous report (Yabannavar et al. 1992) an apparently contradictory behaviour of the fluid flow in the SF bioreactor with important implications to SF performance. Even though a priori one could believe that perfusion flow is the only radial flow across the spin-filter mesh, they observed that higher amounts of fluid seem to cross the filter

screen inwards and outwards. So, in spite of the net flow through the mesh be equal to the perfusion flow rate, they proposed the existence of a higher flow due to recirculation through the SF mesh, which was named exchange flow (Yabannavar et al. 1992).

Deo et al. (1996) made an extensive experimental work and proposed that the ratio of the squared tangential velocity to cell concentration was proportional to the perfusion flux capacity of the spin-filter, which defined as the maximum perfusion flux (perfusion flow rate per mesh area) operable without occurrence of fouling. Thus, higher perfusion flows per mesh area would be feasible for higher rotation rates, evidencing the action of the centrifugal force in avoiding clogging. By increasing the spin-filter rotation in small increments as the cell density increased, Deo et al. (1996) succeeded in scaling-up an optimized 7-L culture to 500-L scale, achieving $> 10^6$ cells mL^{-1} in runs that lasted over 30 days.

In another evidence of the action of the centrifugal force generated by filter rotation, Wereley et al. (2002), using laser-based velocity measurement techniques to study a vortex-flow filter, proposed an operation criterion based on the ratio between the shear force and the Stokes drag. This ratio results proportional to the ratio of the Taylor number to the radial Reynolds number, thus increasing with rotation rate. Based on experimental observations, they claimed that for a force ratio in the order of 20 or greater cake built-up on the filter surface was minimal. However, although giving evidence of the relevance of the centrifugal action, this operation criterion is not totally applicable to mammalian cell retention, since the authors used relatively dense particles (1.6 g cm^{-3}) with diameters much larger ($150\text{--}300 \text{ }\mu\text{m}$) than the mesh opening ($5 \text{ }\mu\text{m}$).

Increases in rotation rate, however, cannot be applied indiscriminately in case of mammalian cell retention, due to the shear sensitivity of animal cells and also because above certain rotation rates clogging of the internal mesh surface has been shown to be enhanced (Trocha et al. 1997).

The tremendous increase in computational power witnessed in the last decades together with the development of high-performance, commercially available computational fluid dynamics (CFD) codes has enabled high-quality numerical simulations of complex systems where transport phenomena are involved. Successful application of CFD to

biotechnological systems range, for instance, from simulations of bioreactors to separation devices (Brucato et al. 1998; Castilho 2001; Medronho et al. 2005). A successful example was the use of CFD to predict the flow field inside a bioreactor (Brucato et al. 1998). The authors were able to reasonably reproduce different velocity profiles obtained by laser doppler anemometry. Castilho (2001) applied CFD to optimize the geometry of a rotating disk filter for animal cell separation. The shear stress was appropriately predicted and the numeric results were confirmed by experiments. In the present work, CFD was employed to study the fluid flow and particle dynamics in an internal spin-filter system.

Materials and methods

The spin-filter bioreactor system

The simulated bioreactor has a 5-L working volume (CMF 3000, Chemap AG, Switzerland) and 200-mm internal diameter. The bioreactor vessel bottom is flat but edges are rounded. Four 29-mm baffles are equally distributed circumferentially to enhance mixing. The vessel has at the bottom a marine propeller with three blades (80 mm diam) and an internal spin-filter (also 80 mm diam), which is supported by an upper independent rotation axis. The SF has a filtration area of 0.04 m² and a filter mesh opening of 20 µm (Betamesh 20, Bopp AG, Switzerland). From the information supplied by the mesh manufacturer, the mesh permeability is

10⁻¹² m². Both the SF sieve and the impeller rotate in a clockwise direction at the same rotation rate.

For simulation purposes, the fluid viscosity and density were set as those of water at 37 °C, taking into account that such properties do not change much compared to real culture medium. The cell density was taken as 1,060 kg m⁻³ and the cell population was considered as having a uniform diameter of 15 µm.

Geometry and computational grid

The computational package used in this work was the commercially available code ANSYS 11 (Ansys Inc., Canonsburg, PA, USA). The bioreactor geometry including the spin-filter was built using the included software Design Modeler. The CFX Mesh tool was used to build the computational grid and the CFD simulations were performed using the CFX software. Personal computers equipped with 3-GHz Intel Pentium IV processors and 3-Gb RAM were used in all simulations.

For modeling purposes, the full geometry was divided in 3 domains (Fig. 1). The first represents the bioreactor without the SF and impeller regions (a), the second corresponds to the SF region (b), and the third to the impeller region (c).

Unstructured computational meshes were generated with increasing resolution for a grid-independence study. The selected mesh had 832135 elements. Any further increase in element number did not result in any change in the predicted velocity profiles, indicating that this grid was sufficiently fine for mesh-independent flow predictions.

Fig. 1 Geometry of the simulated bioreactor showing its three domains: **a** the bioreactor without the spin-filter and impeller regions; **b** the spin-filter region; **c** the impeller region

CFD model: settings and model improvement strategy

Three turbulence models were tested based on their reported success in describing general fluid flow situations (Aubin et al. 2004): the $k-\varepsilon$ and RNG $k-\varepsilon$ models, as well as the SSG Reynolds stress model proposed by Speziale et al. (1991). As no experimental SF data were available for simulation validation, data of a Taylor-Couette system (Wereley and Lueptow 1994) were used to evaluate the physical validity of the results predicted by the three turbulence models. Upon comparison of the simulated and experimental results (data not shown), the SSG model was selected and all simulations showed in the present report were based on it.

The geometry division in three domains (Fig. 1) allowed imposition of rotation motion on domains C and B, while A was left stationary. This is the normal practice for modelling rotational machinery to take into account the periodic motion caused by the presence of impeller blades and baffles (Brucato et al. 1998). The relative motion between the interfaces was treated using the multiple frame of reference protocol with its two variants for steady state simulations (the frozen rotor scheme) and sliding mesh for transient ones (Aubin et al. 2004). Node connection to compensate the absence of one-to-one connectivity was done through the general grid interface (GGI) protocol.

Two kinds of simulations were performed: monophasic, where only the fluid was considered, and multiphasic, comprising the fluid and the dispersed particles. Monophasic simulations were performed in transient mode using steady state results as global field initial condition. In the case of multiphasic simulations, they were limited to steady state mode due to computational power limitation.

Multiphasic simulations were performed using the Eulerian–Eulerian approach. The only terms considered for interphase momentum transfer were the drag force and the Saffman lift force (Saffman 1965). The drag coefficient was set following the Schiller and Nauman (1933) expression and the Saffman lift force coefficient was set constant at 0.5. The radial momentum loss through the filter was modelled using Darcy's law, neglecting the tangential and axial components of the flow velocity through the mesh. The convergence criterion for all simulations was a

Table 1 Full factorial statistical design matrix used to plan the CFD simulations

Perfusion rate (D) (day^{-1})	Normalized perfusion rate (D^*) (–)	Rotation rate (ω) (rpm)	Normalized rotation rate (ω^*) (–)
0.25	–1	109	–1
1.75	+1	109	–1
0.25	–1	325	+1
1.75	+1	325	+1
1.00	0	217	0

maximum squared residual of 10^{-4} and a mass balance error between domains below 0.5%. A cell mass source was included to compensate the cell loss through the outlet.

To evaluate the flow around the SF and the effect of the main operational variables on them, simulations were planned according to a factorial statistical design having as factors the sieve rotational speed and perfusion rate. The ranges studied for both variables were chosen to comprise common values at which the spin-filter bioreactor system has already been operated. No replicates of the central point were carried out, since previous works of the group have confirmed that replicates of numerical CFD simulations yield the same results (Castilho and Anspach 2003). In Table 1, the absolute and normalized values of perfusion rate and rotation velocity used are shown.

Results

The CFD simulations allowed to visualize the flow pattern inside the spin-filter bioreactor system. In Fig. 2, two planar vector plots are shown corresponding to an $r-\theta$ plane mid-height of the filter (Fig. 2a) and an $r-z$ plane halfway between the baffles (Fig. 2b), respectively. In the $r-\theta$ plane (Fig. 2a), it can be observed that the fluid moves following concentric orbits in the close vicinity outside the SF and inside it. Such behavior resembles a Taylor-Couette system. However, it can be seen that the baffles succeed in creating a vigorous fluid mixing disrupting the concentric orbits within their vicinity. In the $r-z$ plane (Fig. 2b), the pumping up effect of the impeller can be clearly observed. Interestingly, it shows recirculation flow, resembling the behavior of Taylor-Couette vortices.

Fig. 2 Velocity vectors corresponding to: **a** r - θ plane mid-height of the filter; **b** r - z plane halfway between the baffles. Simulation conditions: perfusion rate = 1 day^{-1} ; rotation rate = 217 rpm

After checking the basic behaviour of the system, attention was paid to the radial flow through the mesh. In Fig. 3, a snapshot of the filter mesh coloured according to the mass flow direction (inward or outward) across the SF mesh is shown for the condition corresponding to the central point of the statistical design outlined in Table 1.

From Fig. 3, it becomes evident that there is not only an inward flow through the mesh, represented by the darker regions (coloured blue in the online version) with negative mass flow, as it would be expected because of perfusate withdrawal from inside the filter. The regions shown in lighter shading (coloured yellow in the online version) have positive mass flow and thus represent an outward flow across the filter mesh. Therefore, the presence of an exchange flow as experimentally observed by Yabannavar et al. (1992) was theoretically confirmed using the model developed in the present work. It should be mentioned that, as physically expected, the difference between the inward and the outward flow was equal to the perfusion flow, indicating that mass balance was correctly closed.

The values of the radial flow through the filter surface outwards into the bioreactor bulk region are shown in Table 2. These values were calculated from the positive radial velocity data obtained on the mesh surface. It should be noted that the perfusion flow imposed by pumping perfusate from inside the filter ranged in the simulations from 1.4×10^{-5} to $1 \times 10^{-4} \text{ kg s}^{-1}$, whereas the fluid outflow across the mesh found in all simulations was one to two orders of magnitude higher (up to

Fig. 3 Snapshot of the external surface of the SF mesh (contour plot coloured by mass flow) for the central point of experimental design depicted in Table 1. Darker regions with negative mass flow (blue in the online version) correspond to inward flow, whereas lighter regions with positive velocity mass flow (yellow in the online version) correspond to outward flow through the mesh

approximately 130-fold). This indicates how significant the effects of exchange flow might be on mesh fouling.

Table 2 Effect of perfusion flow and rotation rates on radial outflow across the filter mesh

Perfusion rate	Rotation rate	Radial outflow
0.25 day ⁻¹ (1.40×10^{-5} kg s ⁻¹)	109 rpm (1.8 Hz)	3.6 day ⁻¹ (2.10×10^{-4} kg s ⁻¹)
1.75 day ⁻¹ (1.01×10^{-4} kg s ⁻¹)	109 rpm (1.8 Hz)	2.8 day ⁻¹ (1.62×10^{-4} kg s ⁻¹)
0.25 day ⁻¹ (1.40×10^{-5} kg s ⁻¹)	325 rpm (5.4 Hz)	34.1 day ⁻¹ (1.97×10^{-3} kg s ⁻¹)
1.75 day ⁻¹ (1.01×10^{-4} kg s ⁻¹)	325 rpm (5.4 Hz)	29.7 day ⁻¹ (1.71×10^{-3} kg s ⁻¹)
1.00 day ⁻¹ (0.57×10^{-4} kg s ⁻¹)	217 rpm (3.6 Hz)	13.0 day ⁻¹ (7.5×10^{-4} kg s ⁻¹)

The radial flow outwards was calculated from the negative radial velocity data obtained on the mesh surface

From Table 2, it can also be seen that rotation rate strongly influences fluid exchange through the mesh, whereas the perfusion rate has a much less significant influence on it. For instance, the outward flow is one order of magnitude larger when rotation rate increases only threefold.

Taking the normalized values of perfusion rate (D^*) and rotation rate (ω^*), an statistical analysis of their effects on the response (radial outflow) was performed. The perfusion rate and its interaction with the rotation rate were statistically not significant (p -value = 0.05), resulting in an empirical model describing the radial outflow as a linear function of the rotation rate (Eq. 1):

$$Q_{\text{out}} = 16.64 + 14.35 \omega^* \quad (R = 0.984) \quad (1)$$

where ω^* is the normalized rotation rate, R is the correlation coefficient, and Q_{out} is the radial outflow,

expressed as volume of fluid exchanged per bioreactor volume per day (day⁻¹).

Yabannavar et al. (1992) did not give an explanation of the causes behind the exchange flow although they speculated that slipping of the fluid in the laminar sublayers adjacent to the filter or mixing provoked by the filter mesh could be the causes of such phenomenon. Nevertheless, they recognized that a more fundamental fluid mechanics study was needed to really understand the cause of this phenomenon.

To explore the possible causes of the exchange flow, streamlines were drawn in the same r - z plane shown in Fig. 2b. As can be seen in Fig. 4a, several vortices are present. Such behavior has been extensively reported in Taylor-Couette systems operating in supercritical regime (di Prima and Swinney 1979). However, to the best of our knowledge it has never been reported to occur in an internal SF system. The

Fig. 4 Streamlines on an r - z plane dividing the bioreactor in the middle, halfway between the baffles (perfusion rate = 1 day⁻¹ and rotation rate = 217 rpm): **a** complete plane showing streamlines in the whole bioreactor; **b** zoom of the internal and external regions surrounding the SF mesh

height of each vortex is roughly equal to the annular gap size as expected in Taylor-Couette systems, which adds physical consistency to these results.

More interestingly is to observe in Fig. 4b that the vortices are not limited to the external region and, due to inertia, effectively penetrate the inner volume of the SF. This finding is thus an evidence that the presence of this vortical motion around the mesh is the most probable cause for the exchange flow to occur. Differently from a Taylor-Couette system, where the vortices are all limited to the annular gap region, in the internal spin-filter bioreactor system the rotating cylinder is not a solid wall, but rather a permeable filter mesh, allowing the vortices to penetrate the filter and thus explaining the high levels of inward and outward flow observed in the present work.

Lateral particle migration is another phenomenon that has been argued to have an influence on SF performance (Yabannavar et al. 1992; Vallez-Chet-reanu 2006). In order to investigate this phenomenon in the system under study, an r - θ plane crossing the mid-height of the SF was coloured by cell concentration (Fig. 5).

Figure 5b shows that cell concentration is significantly reduced in the close vicinity of the rotating filter mesh. Cell concentrations very close to the mesh are decreased approximately to the half of the bulk concentration. Such a depletion of cells in the vicinity of the sieve is consistent with the lateral migration observed in Taylor-Couette flow (Halow and Wills 1970). Therefore, it can be stated that the

CFD model predicts the occurrence of lateral particle migration.

Although for pure Taylor-Couette flow an increase in particle concentration at the outer static wall is expected, the presence of baffles in the SF system under fully turbulent flow conditions is expected to homogenize the culture at radii far from the mesh. It can also be seen that certain accumulation of cells occurs in the regions behind the baffles due to the presence of the recirculation zones previously shown in Fig. 2a.

From the CFD data used to construct Fig. 5a, a separation efficiency of approximately 94% could be calculated, which is in the range expected for SF efficiencies. It is interesting to note that the quite high exchange flow through the mesh (13 times higher than the perfusion rate under the simulation conditions of Fig. 5) seems not to affect the separation efficiency, corroborating with the observation of a depletion of cells in the vicinity of the sieve.

In the model employed in this study, the Schiller-Nauman drag force and the Saffman lift force were used to calculate the motion of the cells. The radial force originating from the sum of the radial components of both forces (drag and lift force) in an r - θ plane is shown in Fig. 6, with positive values indicating that the resulting radial force acts outwards and negative values standing for a radial force acting inwards.

It can be observed in the outer region, but far from the filter, that the radial force acting over the particles is quite small. However, near the mesh this radial

Fig. 5 Cell concentration on an r - θ plane at mid-height of the SF, for a rotation rate of 217 rpm and a perfusion rate of 1 day^{-1} . **a** whole r - θ plane; **b** zoom of the r - θ plane close to the filter vicinity. Filter thickness has been shadowed in **a** black, and **b** gray

Fig. 6 Plane r - θ at mid-height of the filter coloured by the radial force, defined as the sum of the radial components of the lift and the drag forces. Simulation conditions: rotation rate = 217 rpm; perfusion rate = 1 day^{-1} . Filter thickness is shown in gray

force is definitively positive in sign and increases almost an order of magnitude with respect to the highest values in the bulk of the fluid. As the radial force is in this case pointing outwards, the cells do experiment a movement which directs them away from the mesh. This can explain the lateral particle migration observed in Fig. 5b in the vicinity of the outer surface of the filter.

In the inner bulk region (note the scale on the right hand side of Fig. 6), the resulting radial force is much smaller (ca. $4.5 \times 10^{-15} \text{ N}$) and directs the cells gently towards the internal surface of the SF. However, in a thin region (that is narrower than the equivalent region adjacent to the outer surface of the mesh), the radial force becomes negative, directing cells inwards and thus also contributing to deplete cells from the internal vicinity of the mesh. The fact that in the inner region the force is approximately one order of magnitude lower than in the outer region, associated to the fact that cell concentration inside the SF is much lower, might explain why there seems to be no lateral migration in the region inside the filter (Fig. 5). As the distance from the mesh increases, the radial force rapidly decreases in both directions. This occurs because the lift force is mainly dependent on the shear rate, which is only significant near the filter mesh, assuming very low values in the bulk regions.

Discussion

The CFD ability to correctly model the flow field in a SF system was verified by similarity against data from Taylor-Couette systems. Since large tangential velocity gradients exist in the radial direction near the rotating filter wall and since a SF is intended to be used in animal cell culture, it is relevant to calculate the maximum wall shear stress present in the system that could eventually be detrimental to the cells. The shear rates calculated in the current study were between 100 and 200 s^{-1} , resulting in a shear stress below 0.2 Pa, which is much lower than shear levels reported as being detrimental to animal cells (Castilho and Anspach 2003).

It is interesting to note that the phenomenon of lateral particle migration that has been for long assumed to have an influence on the SF performance was concretely shown to occur through numerical simulation. Lateral migration helps to explain why spin-filters with mesh sizes larger than the average cell diameter may exhibit retention efficiencies above 90% (Vallez-Cheteanu 2006). Thus, the present results help to understand why cell size exclusion by the filter mesh is not the only mechanism responsible for cell retention in SF systems.

Experimental results at very high particle concentration showed that particle migration could reduce the disperse phase concentration up to 10 times near a solid rotating wall for a Taylor-Couette system (Tetlow and Graham 1998). Such a decrease is consistent with the depletion calculated from the present CFD simulations (2 times lower), since in the current case there is a radial drag due to perfusion acting on the cells. Therefore, the radial resultant of the lift and drag force exerted over the particles explains why cell depletion occurs in the vicinity of the SF mesh and why it is not so pronounced as in Taylor-Couette systems, which have a solid rotating cylinder.

It is also interesting to note that the order of magnitude of the radial force predicted by the CFD model developed in this work ($\sim 10^{-13}$ – 10^{-14} N) is comparable to that of adhesion forces reported by Curtis (1967, *apud* Favre and Thaler 1992) for blood cells, although cell adhesion mediated by DNA may be stronger (Mercille et al. 1994). Thus, under certain conditions it could be expected that hydrodynamic forces might even counteract the adhesion forces,

preventing or diminishing SF clogging. More sophisticated CFD approaches are required to take into account cell adhesion forces due to the fact that their values are significant only at very small distances from the SF mesh (below 0.1 μm).

The CFD calculations done in this work revealed that the ratio of lift force to drag force near the mesh is approximately 30. A ratio of 20 for these two forces was experimentally detected to yield minimal particle deposition and cake formation on the mesh surface of a rotating filter device (Wereley et al. 2002). Although the expressions employed to estimate both forces are different in both works and despite the differences regarding the filter system, particle properties and mesh sizes, the similarity of both values may indicate the ratio of both forces (lift/drag) as an interesting factor to be further investigated regarding spin-filter operation.

Another relevant result obtained with the CFD model developed in the present work is the detection of a bidirectional radial flow through the filter mesh, which is between 1 and 2 orders of magnitude higher than the perfusate flow. As this exchange flow increases with increasing rotation rate, special care must be taken to avoid setting too large rotation velocities.

The results revealed that perfusion flow does not have a significant impact on the exchange flow. However, as SF mesh gets slowly clogged, the relative magnitude of the exchange flow will probably diminish due to local decreases in permeability and perfusion flow may turn to be more important. Thus, deeper studies are needed to develop criteria regarding the effect of perfusion rate on the long-term performance of the SF.

Regarding the sieve rotation, it affects both the exchange flow and the lateral migration of particles. Since exchange flow directly affects the drag force, and because lateral migration is closely related to the lift force, this is a further indication that a possible optimization approach could be related to the radial balance of these two forces.

The correct simulation of lateral migration and fluid exchange through the mesh using CFD is quite encouraging. It can be concluded that CFD is a very valuable tool for process optimization of spin-filters, provided it is properly validated against experimental results and good simulation practices are observed.

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