iJRASET
International Journal For Research in
Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 5 **Issue:** X **Month of publication:** October 2017

DOI: http://doi.org/10.22214/ijraset.2017.10236

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor:6.887
Volume 5 Issue X, October 2017- Available at www.ijraset.com

Analysis of Oxygen Concentration Equation in Multi Cell Tumour Spheroid

Mohammed Arshad Ali[1], Ahmed Waheedullah[2]
[1]*Associate Professor, Department of Business Management, Deccan school of management, Hyderabad.*
[2]*Retired Professor, Department of Mathematics MJ college of Engineering & Technology, Hyderabad.*

Abstract*: Cancer is one of the leading causes of death all over the world. Cancer occurs at different parts of the human body causing abnormal and uncontrolled growth of the tissue. Treatment of the cancer depends on the location, stage and nature of the cancer tumour. InVitro experiments were conducted with Multi cell tumour spheroids for finding characteristics of the tumours. Oxygen is the vital element in growth of the tumour along with other elements. Mathematical models helped these In vitro experiments in comparing observed results and estimating unknown characteristics of the Tumours. In this paper, the behaviour of Oxygen concentration equation obtained by using the Diffusion theory with the spherical membrane of the Multi cell Tumour Spheroid is studied at different situations theoretically whose results were similar to the experimetal results .
Keywords*: Multi cell tumour spheroid, MCTS, Oxygen distribution in MCTS, Mathematical modelling of tumour spheroid, Tumour growth models.

I. INTRODUCTION

Multi cell tumour spheroids (MCTS) are bunch of similar type of tumour cells in spherical form. Multi cell tumours are widely used in cancer research to study the characteristics of tumours, reasons for their growth and in treatment of cancer to investigate the effects of radio therapy and chemotherapy. The studies related to multi cell tumour spheroids date back to late 1960's. Growth of multi cell tumours were examined by Burton A.C. (1966), Judah Folkman and Mark Hochberg (1973), H.P. Greenspan (1973), R.M. Sutherland (1974), W. Muller (1981), Mueller and Klieser W. (1984), Freyer J.P , Sutherland RM (1986), Freyer J.P (1988) etc. Multi cell spheroids are considered as alternatives to monolayer cultures of in vivo tumour growth experimental models. Still, the experiments using multi cell tumour spheroids were going on and experiments would continue as long as the research on cancer continues. Studies were conducted on multi cell tumour spheroids with different culture methods using various techniques and their results were available about their behaviour.

II. EXPERIMENTS WITH MCTS

Generally multi cell tumour spheroids are studied by suspending a few live tumour cells in a vessel containing a liquid medium which provides a suitable growth environment for the tumour cells. In the case of James M. Freyer and Robert M. Sutherland (1986), EMT6/Ro mouse mammary carcinoma cell spheroids cultured in large spinner flasks containing the medium with appropriate Oxygen and Glucose concentrations. According to Judah Folkman and Mark Hochberg (1973), used B-16 mouse melanoma, V-79 Chinese hamster lung and L-518Y murine leukemia cells were planted in soft agar of Fischer's medium containing Noble agar, horse serum mixed with antibiotics were cultured in Falcon flasks gassed with carbon dioxide. During the experiment, these multi cell tumour spheroids had gone through three different phases of growth. In the beginning, proliferation of the cells took place forcing the spheroid to grow at an exponential rate. As the spheroid size increased due to proliferation, insufficient nutrition at inner regions caused proliferation to slow down where the growth rate was linear. A dead cell mass formed in the end at the centre of the tumour spheroid is known as Necrotic region. Finally, the tumour spheroid reached its steady state size showing a three layer structure consisting of Necrotic region in the centre, a middle layer with living but non-proliferating cells and an outer thin layer of proliferating cells.

III. MATHEMATICAL MODELS OF MCTS

Mathematical models have been developed by considering the behaviour of multi cell tumour spheroids *In vitro* experiments using diffusion theory. Burton A.C (1966) developed a model using diffusion theory and showed that the growth of solid tumours is not exponential but it follows Gompertzian relation. The diffusion-Limitation theory developed by Burton A.C (1966) predicted critical tumour radius where necrosis appears, the thickness of the viable dividing critical layer having a constant of 58% of the critical tumour radius for necrosis and the theory is consistent with Gompertzian relation for growth of small tumours. Another model developed by Deakin (1974) considered the spheroids that were grown in normal medium suspension culture. This model proposed that the Oxygen concentration was constant above a critical value. The variable rim thickness of the spheroid as a function of necrotic radius was parameterized by this model that agreed well with experimental values.

IV. MATHEMATICAL MODELING OF OXYGEN DISTRIBUTION IN MCTS

A. Assumptions

1) The multi cellular tumour spheroid is considered to be a sphere and any variables of interest are functions only of the radial coordinate r .
2) The concentration of oxygen at the surface of the tumour spheroid $r = R_0$ is given by C_0 and is independent of the size of the tumour spheroid
3) Since formation of necrotic core is closely related to lack of oxygen, the oxygen is considered as vital nutrient even though other nutrients to some extent required for survival of cells
4) the living cells consume oxygen at a constant rate A per uit volume per unit time.

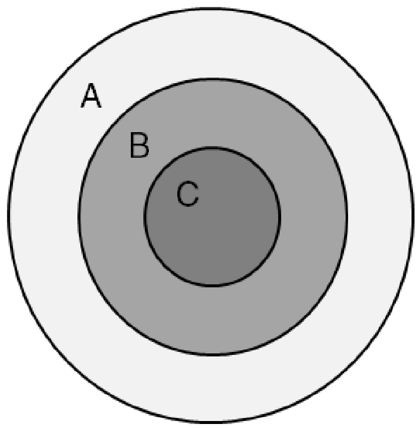


Figure 1.Diagrammatic representation of three layer structure of tumour spheroid.

B. Diffusion Theory

Diffusion is a natural mass transportation mechanism that moves matter from an area of higher concentration to those of lower concentration. The formation of necrotic region in the tumour spheroid can be explained by diffusion theory. In diffusion the macroscopic transport of matter is observed to move from a region of higher concentration of substance to the areas of lower concentration. The diffusion occurs to balance the concentration at two regions such as heat flows from regions of higher temperature to regions of lower temperature to equalize temperature variation.

C. Oxygen Distribution Equation

The concept of diffusion theory was applied to model diffusion of oxygen in multi cellular tumour spheroid which is almost in spherical shape by making some assumptions and limitations. Diffusion of oxygen in tumour spheroid was studied by considering a thin circular frame of tumour spheroid of thickness Δr which is at a distance r from the centre of the tumour spheroid (Figure 2).According to Fick's law the amount of oxygen consumption flowing into this frame at a distance r in unit time is given by (The flow of oxygen per unit area in unit time) × (the area available) The oxygen consumed in the frame in unit time can be obtained by (The amount of oxygen which flown into the frame in unit time) − (The amount of oxygen which flown out from the frame in unit time).The amount of oxygen consumed in the frame in unit time can be obtained by (Rate at which oxygen is consumed per unit volume in unit time) × (Volume of the frame). The second order differential equation for the Oxygen concentration in C is $\frac{D}{r^2}\frac{d}{dr}\left[r^2\frac{dC}{dr}\right] = A$, where D , is the diffusion coefficient. The concentration of Oxygen at a distance r from the centre of the sphere will be $C(r) = C_0 + \frac{A}{6D}(r^2 - R_0^2)$

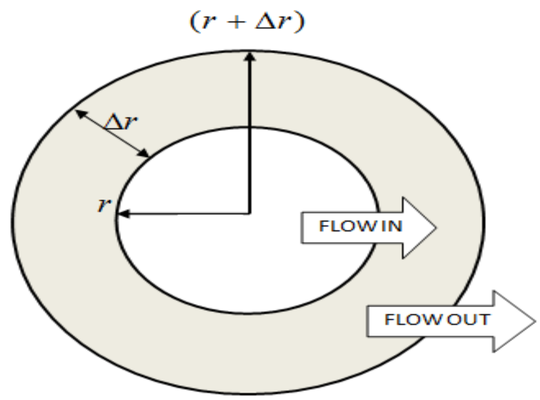


Figure 2.Diagrammatic representation of Oxygen flow in a circular rim.

V. BEHAVIOUR AND ANALYSIS OF OXYGEN CONCENTRATION EQUATION

The behaviour of equation $C(r) = C_0 + \frac{A}{6D}(r^2 - R_0^2)$ is studied by giving values of different Oxygen consumption rates A, diffusion coefficients D and initial Oxygen concentration at outer surface of the tumour spheroid. MATLAB is used for studying the effect of variables with the following initial values. $r = [0, 25]; C_0 = 300; D = 1.75,\ A = 5,\ R_0 = 25$. (Figure 3).

The Oxygen concentration levels in the tumour spheroid can be seen by increasing the diffusion coefficient from 1.75 to 3.75 (Figure 4). The effect of increasing the Oxygen consumption rate A, on Oxygen concentration levels can be observed from the following graph when A takes values from 3.00 to 5.00 by keeping D at constant value 3.0 (Figure 5).

The Oxygen concentrations at different points of the tumour spheroid can be compared in normal situation along with increasing values of diffusion coefficient and increasing values of Oxygen consumption rates. In this case $A = 3$ and $D = 1.75$.(Figure 6). In a particular case at the centre of the spheroid, by taking $r = 0$, the Oxygen concentration equation will become $C(0) = C_0 - \frac{A}{6D} R_0^2$.

The Oxygen concentration at the centre is dependent on the outer radius of the sphere. The behaviour of the equation can be seen in the graph (Figure 7). In the diagrammatic representation of three layer structure of tumor spheroid, the region C represents necrotic region full of dead cells. The region B represents live but proliferating cells. The region consists of proliferating cells. The dead cell necrotic region will have very low Oxygen concentration due to lengthy distance from its outside surface. The low level of Oxygen in this region cannot is sufficient for proliferation. The other two regions will have higher concentrations than the inner region and more it moves towards the outer surface, the Oxygen concentration increases. The phenomenon is observed in the graph (Figure 8).

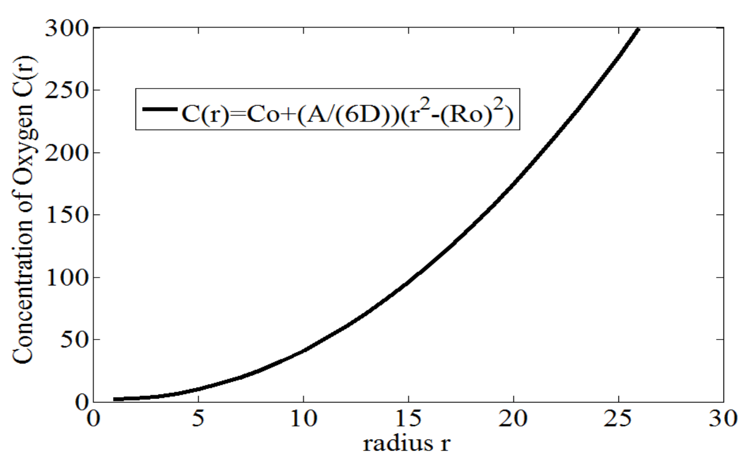


Figure 3.Graph of Oxygen distribution in tumour spheroid.

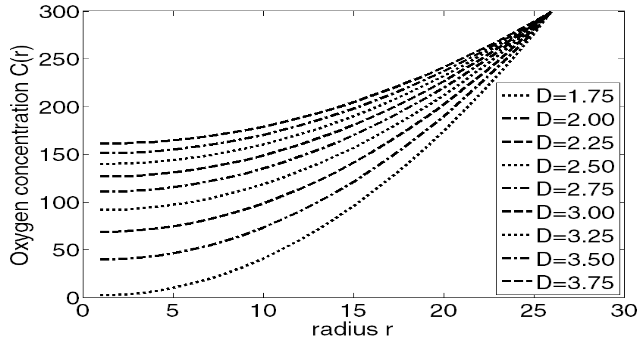


Figure 4.Graph of Oxygen distribution in tumour spheroid for different increasing values of diffusion coefficient D.

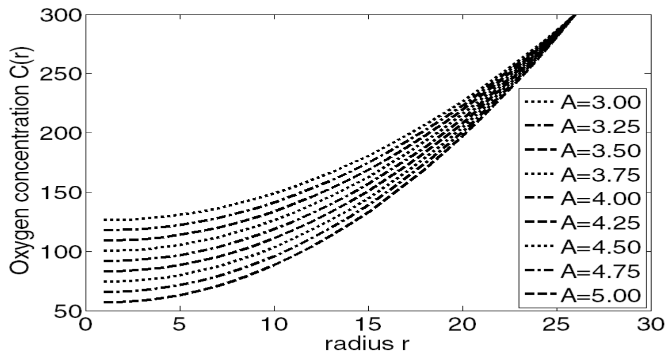


Figure 5.Graph of Oxygen distribution in tumour spheroid for different increasing values of Oxygen consumption rates A.

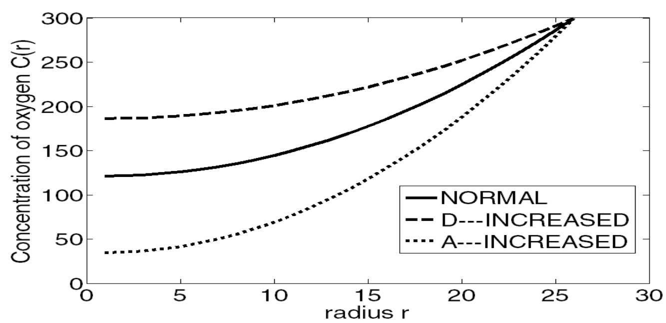


Figure 6.Graph of Oxygen distribution in tumour spheroid for Normal and different increasing values of diffusion coefficient D and Oxygen consumption rates A.

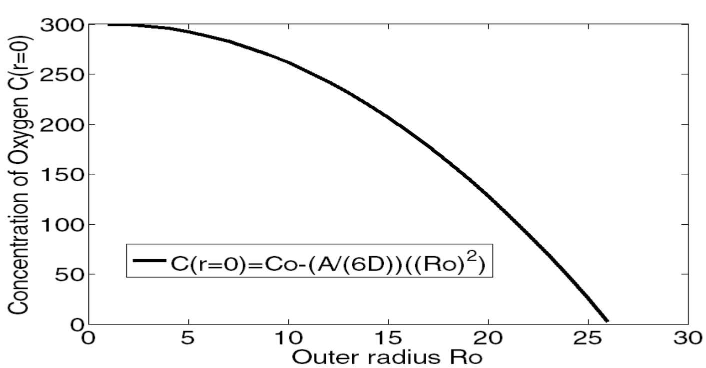


Figure 7.Graph of Oxygen concentration at the centre of the tumour spheroid.

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor:6.887
Volume 5 Issue X, October 2017- Available at www.ijraset.com

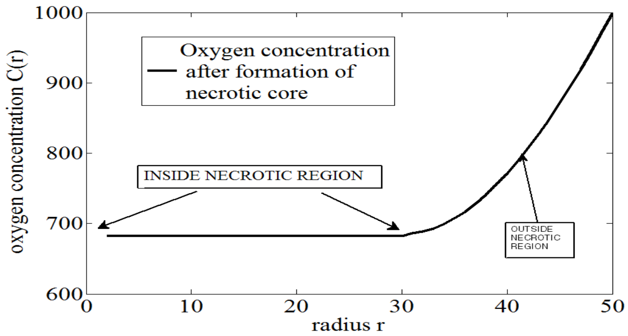


Figure 8.Graph of Oxygen distribution in tumour spheroid after formation of necrotic core.

V. CONCLUSIONS

From the above discussion, following conclusions can be drawn about the Oxygen concentration in tumor spheroid.

A. If the Oxygen concentration C_0 outside the surface of the sphere is increased by a certain amount, then the Oxygen concentration throughout the sphere is increased by the same amount.

B. From figure 3, the concentration of Oxygen is increasing when the radius is increasing. That means the concentration of the Oxygen is increasing when it is moving away from its centre. The more it approaches towards its centre, the Oxygen concentration will be less.

C. If the diffusion coefficient D is increased, the Oxygen concentration inside the tumour spheroid is increased (Figure 4) and if the rate of consumption of Oxygen A is increased, the Oxygen concentration inside the tumour spheroid is decreased. The concentration of Oxygen is inversely proportional to the rate of consumption of Oxygen (figure 5).

D. From figure 6, it is clearly evident that the concentration is increased at every point as compared to normal parameter values with the increase of D and the effect is reverse with higher values of Oxygen consumption rates A.

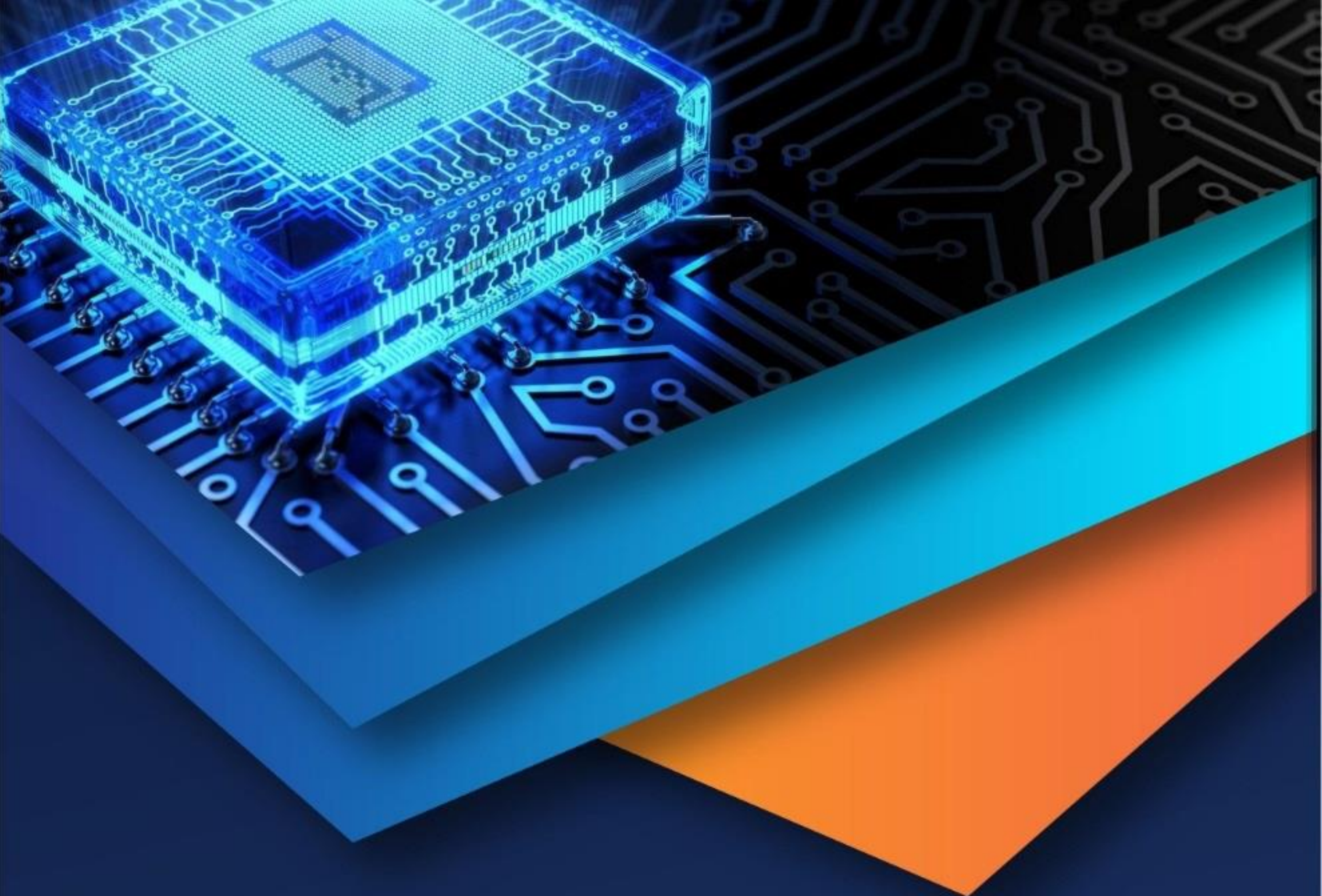
E. When the radius of the tumour spheroid is very small, the concentration of Oxygen at the centre of the spheroid will be same as that of outside concentration.

F. Experimental results are similar to the behaviour of Oxygen concentration equation after formation of necrotic core. Due to dead cells in the necrotic region, it is showing constant Oxygen concentration in the necrotic region. But outside the necrotic region, the regions A & B are full of live cells with proliferating and non proliferating cells. The concentration outside the necrotic region is increasing as it is moving towards the outer surface.

REFERENCES

[1] A.C. Burton, Rate of growth of solid tumours as a problem of diffusion, Growth **30**(1966), 157-176.
[2] A.S. Deakin, Model for the growth of a solid in vitro tumor, Growth **39**(1975), 159-165
[3] Folkman J, and M. Hochberg, (1973), Self regulation of growth in three dimensions. J. Exp .Med 138:745-753.
[4] Freyer JP, Tustanoff E, Franko AJ ,Sutherland RM, In situ Oxygen consumption rates of cells in V-79 multi cellular spheroids during growth. J Cell Physiol (1984) Jan; 118(1):53-61.
[5] H.P. Greenspan, Models for the growth of a solid tumor by diffusion, Stud.Appl.Math.52 (1972), 317-340.
[6] H.P. Greenspan, On the growth and stability of cell cultures and solid tumors, J. Theor. Biol.56 (1976), 229-242
[7] Sutherland R.M, and R.E Durand (1976). Radiation response of multi cell spheroids - an in vitro tumor model. Curr.Top.Radiat Res 11:87-139.
[8] James P. Freyer and Robert M. Sutherland, Regulation of Growth saturation and Development of Necrosis in EMT6/R_O Multi cellular Spheroids by the Glucose and Oxygen Supply. Cancer Research 46, 3504-3512.
[9] Spheroids in Cancer Research-Methods and Perspectives. (**Acker**, H., **Carlsson**, J., **Durand**, R., **Sutherland**, R.M), Springer-Verlag (1984).

Note: Above article is the part of the research work carried out for PhD course curriculum under Osmania University in the Dept of Mathematics.



10.22214/IJRASET

INDEX COPERNICUS
45.98

ISRA JIF
IMPACT FACTOR:
7.129

TOGETHER WE REACH THE GOAL
IMPACT FACTOR:
7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY