

Bangalore,
March 22, 2004

**Dr. A.K. Singhvi,
Sr. Professor, Planetary & Geosciences Division
Physical Research Laboratory
Navrangpura, Ahmedabad 380 009
INDIA**

Subject: Submission of revised progress report (SR/FTP/MS-12/2001)

Dear Prof Singhvi,

Received your letter dated February 3, 2004. I am enclosing you my progress report (in the DST format) which is a revised and expanded version of the handwritten one. I also enclose reprints of my papers published /in press. Please find the same. I am sorry to disappoint you regarding my report. Please find my explanations below.

1. I agree that I sent the report not in time. I accept my mistake and sorry for the same. I wanted to include the status of two of my manuscripts which were submitted more than a year ago. I was expecting a reply fro the editor anytime, hence the delay.
2. Even though you have mentioned the font size to be used in your letter, in the report format enclosed with your letter, it was clearly stated on the first page of the form that "Manuscripts should be neatly written/ printed (with single spacing)...". Latest forms soft copies of the format available also have option for clearly handwritten option.
I have now typed the format according to the font size you have mentioned and enclose with this letter.
3. Rs. 20 lakhs was mentioned as expenditure in my previous report. I agree with this mistake. This is a 'typographical error' and now I am providing correct figures in the report enclosed.
4. I am sorry that I didn't come to present at the workshop. However, I do not know sincerely that it is an obligation to personally come to present the report. If I known this earlier, I would have certainly shifted my teaching timetable.

I strongly object your statement that I am not serious about the project, based on above points. It is unfortunate that my publication track record in the project period was not at all considered while making such judgment. Usually in good scientific academic Institutes, research work is judged by the publications and results obtained and not solely by the method of report submitted i.e. by hand written, submitted personally etc.

Apart from the papers published / in press which I have mentioned in the report, two additional papers were accepted since January 2004 and the details of these are as follows:

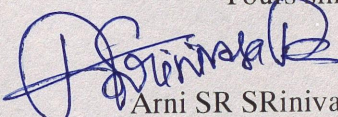
- 2004 - **Rao A.S.R.S**
U type functions
Bulletin of Informatics and Cybernetics (In press)
(Formerly *Bulletin of Mathematical Statistics*)
- 2004 - **Rao A.S.R.S and Kakehashi, M**
A Combination of differential equations and convolution in predicting an epidemic
Sadhana - Proc. Ind. Acad. Sc, Engg (accepted)

I am also enclosing my project report and copies of all the papers to The Chairman CES, The Director IISc and DST to bring their attention about my commitment to research.

May I request you to grant the project funding by taking into consideration above facts. I will certainly present my progress report in the next meeting.

Thanking you.

With best regards,
Yours sincerely,


Arni SR SRinivasa Rao

Centre for Ecological Sciences
Indian Institute of Science
Bangalore 560 012

Copies to

1. Dr. R.C. Srivastava, Scientist-G, DST, New Delhi
2. Dr. S. Sudershan Rao, Scientist-C, DST, New Delhi
3. The Director, IISc, Bangalore
4. The Chairman, Centre for Ecological Sciences, IISc, Bangalore
5. Prof C.E. Veni Madhavan, IISc, Bangalore

PROGRESS REPORT

1. Project Title: Mathematical and Statistical Modeling for the epidemiological clinical & virological data for HIV/AIDS	DST No: SR/FTP/MS-12/2001
2. PI (Name & Address): Arni SR Srinivasa Rao Centre for Ecological Sciences Indian Institute of Science Bangalore 560 012	Date of Birth January, 10 , 1972
3. Co-PI (Name & Address): NIL	Date of Birth
4. Broad area of Research: Mathematical Sciences 4.1 Sub Area: Mathematical Biology	
5. Approved Objectives of the Proposal : 1. Developing risk-type mathematical models for spread of AIDS in India. 2. Estimating the parameters of incubation distribution of AIDS based on disease progression and co-factors responsible for the same. 3. Proposing models for the Anti retroviral therapy and if data permits then testing the same.	
Date of Start: August 1, 2002	Total cost of Project: Rs.840000.00
Date of completion: Report as on December 1 , 2003 (Total 11 months excluding 5 months leave sanctioned by DST to visit abroad)	Expenditure as on <u>Dec1, 2003</u> : Rs. 288196.00
6. Methodology : My work in this report period involved theoretical investigations on both the basic as well as applied aspects of AIDS epidemiology. A set of non-linear dynamical models for the spread of AIDS was developed. Let $\zeta(t)$ be the function that was used to describe the HIV density, while the distribution of incubation periods was assumed to be $\Gamma(t)$. The cumulative distribution of AIDS cases is thus seen to be a convolution of these two functions. Using	

deconvolution techniques on the cumulative distribution based on the available data, the parameters of the distributions describing HIV density and incubation periods were estimated. This above method was performed to estimated parameters using *exponential, logistic and gamma* incubation distributions. For each distribution *likelihood equation* was constructed.

A definition for *efficiency function* of reported disease cases in general was given. This definition can be taken as efficiency of reported AIDS cases. Using this function and using convergence principles, limiting properties of such function was studied. This study also extended by taking reported cases as a *Poisson process*.

From the applied aspects, immunology data was taken from an ICMR office in Pune. A relation between ALC (absolute lymphocyte count) and CD4 counts among HIV people was studied. Taking CD4 as a dependent variable and using multiple regression techniques a linear relation between above variables for Indian samples was obtained, which will predict CD4 value given a ALC value.

7. Salient Research Achievements:

7.1 Summary of Progress

The basic model was formulated and consistency checks were completed. The model was further developed to make it more realistic (do not say 'tried to introduce') by including two more facets:

- (i) behavioural changes
- (ii) transmission probabilities

This Model explained mechanisms of transmission of virus from risk group of females to adult males and *vice versa* in the population. Here behavioural changes include withdrawal rate from the high risk nature, usage of condoms etc. Transmission probabilities can be classified as a) transmission of HIV by an individual with STD (sexually transmitted disease) b) transmission of HIV by an individual without STD c) transmission of STD by an HIV individual and d) transmission of STD by an individual without HIV. Difficulties relating to estimating sub – populations who are at risk are also important concern. Modelers need to incorporate accurate estimates of sub populations if the aim is to predict infection level in the sub population. Different ways to estimate indirectly sub population sizes were also highlighted in the above model building. Hence, survey methodologies and designs implemented to obtain HIV number through various agencies in India were studied and caution to be taken while using data arise from such sources while predicting Indian HIV scenario was pointed out. Two papers on above modeling aspects and related discussion were published.

Mathematical analysis of reported disease cases was carried out by proving three theorems. This was primarily done by using a function which I have defined. As it was briefly described above in methodology part, this function measures the rate of reporting of reported disease cases to total disease cases. Sequences of diseases over time period converge or diverge was studied using Poisson probability process. If R , reported cases is always under-reported and the efficiency function is non decreasing then it was found that sequence (R_n) is converges. Similarly, if sequence (R_n) is decreasing and sequence of efficiency function increases over time, then it was proved that total reported cases, (T_n) is convergent. If

sequence (R_n) follows Poisson process then sequence (T_n) is proved as a divergent sequence.

Incubation period parameters were estimated using deconvolution method and with the help of EM algorithm. The length of the incubation period and the HIV infection are assumed to be independent variables. Now the distribution of cumulative AIDS was represented as a convolution of the above two functions. Fixing a plausible range of infection density parameter values and from the reported AIDS cases, we estimated parameters of the incubation distribution through method of maximum likelihood estimation.

The model and method that is implemented here will be valid for predicting any country's data if that suits our parameter definitions. Though gamma function can mimic several exponential forms, it is suggested in this work Weibull is preferred model incubation period due to flexible shapes. Apart from this Weibull is simple computationally if we are dealing with cumulative functions.

In the analysis with convolution technique (also known as back-calculation method in AIDS epidemiology), there was some ambiguity on the assumptions on the distribution of 'incubation time.' Actually it must be the time between report of HIV infection and that of AIDS development in our analysis. We considered some variety of the distributions and saw its effect on the prediction. The prediction on the number of AIDS cases was not so sensitive to the distribution. Truncation effect in the incubation distribution was not found significantly.

For the third objective basic data analysis was carried out (jointly) with immunologists in the country. A manuscript is under preparation which explains the basic relation obtained between ALC and CD4 cells in the body. If established this relation firmly, then it will be of great advantage for the low-tech countries where GDP per capita is low.

7.2 New Observations:

In earlier dynamical models which were used in predicting epidemics, usually it was standard practice to take parameter values from experimental evidence, guess work or through simulation. Such practice normally works well when there is enough research evidence. Through this project work, it was observed that generation of parameters could be possible by constructing likelihood functions and using maximizing algorithms. We also obtained an important relation between ALC (a marker for HIV) and CD4 cell count in the body based on clinical data.

7.3 Innovations:

NIL

7.4 Application Potential:

7.4.1 Long Term

The dynamical models developed here which incorporates transmission dynamics of heterosexual mode of transmission can be suitably extended by incorporating additional term on vaccine efficacy. This will be useful to understand effect of vaccines in the population level.

7.4.2 Immediate

CD4 diagnosis costs in India are relatively very high comparing with ALC diagnosis costs. As CD4 is best marker for HIV disease status, it is important to get it diagnosed. Usually patients skip regular CD4 testing due to this high costs. ALC count can be taken as a surrogate marker of HIV. Testing costs for ALC in India is very economical and hence many people with HIV in India who are from low income group can spend money for testing their status. This should help eventually for good adherence of HIV drugs available in the market.

7.5 Any other

Theoretical result that deconvolution technique was found to be helpful in getting some of the key parameters in the dynamics. This method could also be used in epidemics where incubation period is large and variable.

8. Research work which remains to be done under the project (for on-going projects)

Data Analysis in support of virus dynamics is to be begun in next few months. We have arrived at some weak relationship between ALC and CD4, and we need to now work on mathematical model for this relationship. Prevention models are to be tested by fitting real data obtained from various government and non-government bodies/institutions. Delay differential models have to be analytically shown to express intracellular delay in HIV dynamics.

Ph.Ds Produced no:	Technical Personnel trained:	Research Publications arising out of the present project:
NIL	NIL	5 Published / in press

List of Publications from this Project (including title, author(s), journals & year(s))
 (A) Papers published only in cited Journals (SCI)

Before December 1, 2003 and after commencement of the project in August 2002.

- 2004 - **Rao A.S.R.S**
Limiting theorems on case reporting.
Applied Mathematics Letters (In Press)
- 2004 - Kakehashi, M and **Rao, A.S.R.S.**
Mathematical and statistical approaches to risk management for the prevention of HIV/AIDS and other infectious diseases.
Journal of Medical Safety (in press)
- 2003 - **Rao A.S.R.S and S. K. Hira**
Evidence of shorter incubation period of HIV-1 in Mumbai, India
International Journal of STD & AIDS
 (Royal Society of Medicine, London), 14: 499 - 500.
- 2003 - **Rao A.S.R.S**
Can we obtain realistic HIV/AIDS estimates in India?
Journal of Biosciences, 28, 4: 367 - 9.
- 2003 - **Rao A.S.R.S**
Mathematical Modelling of AIDS Epidemic in India
Current Science, 84, 9: 1192 - 7.

(B) Papers published in Conference Proceedings, Popular Journals etc.
 NIL

Patents filed/ to be filed: NIL

Major Equipment (Model and Make)

S No	Sanctioned List	Procured (Yes) Model & make	Cost (Rs in lakhs)	Working (Yes/ No)	Utilisation Rate (%)
1	Pentium IV PC & Printer	Assembled Samsung Monitor Samsung Printer	0.54	Yes	100

INDIAN STATISTICAL INSTITUTE



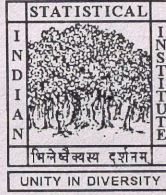
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11 March, 2008.

Professor N. V. Joshi,
Centre for Ecological Sciences
Indian Institute of Science
Bangalore 110001

Dear Professor Joshi,


Trust this finds you well.

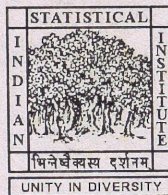
Please find enclosed CD consisting of E-books in Statistics which includes the book on Demography and Ecology which I mentioned to you earlier. I was sorting out all my files and realised that I didn't send you this book as promised.

With best regards,

Arni S.R. Srinivasa Rao

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26 June, 2008

Dear Professor Joshi,

It is my pleasure to enclose you some of my recent papers. Thank you very much for your encouragement. Hope you are doing well.

With warm regards,

Rao