Box 1. Projects for implementation.

_CaFICA (Carbon fluxes in India and Central Asia)_

CO₂ fluxes play a central role in issues like global warming and modelling of climate-change scenarios. The CaFICA project aims to improve our knowledge of the CO₂ sources and sinks over India and Central Asia through a high-precision CO₂ monitoring (for example, at the Indian Astrophysical Observatory at Hanle) to interpret the observed variations and to develop methods of assimilating the continuous CO₂ time series.

_LICOS (Life cycles of convective systems)_

The objective of the LICOS project is to gain understanding of the processes which govern the life cycle of tropical convective systems, especially those linked to the monsoon.

_MOTIVE (Monsoons and the intraseasonal-interannual variations experiment)_

MOTIVE aims to improve our knowledge of the predictability of the Indian Ocean monsoon and the ability of GCMs to represent this predictability. This project is associated with the development of climate modelling and with in situ experiments to improve our understanding of the intra-seasonal oscillation activity over the Indo-Pacific region.

_RIO (Resources in the Indian Ocean)_

The objective of RIO is to understand the main processes controlling marine resources in the open sea of the Indian Ocean, and develop a modelling approach ready to be used in forecast mode for fisheries, to be translated to methodology for identification of potential fishing zone and long-term policy planning.

_VAMOS (Variational assimilation in meteorological and oceanic systems)_

This project concentrates on theoretical aspects of variational assimilation, such as a posteriori evaluation, identification of model errors, effective use of the adjoint solution and physical assimilation. The objectives are to use variational assimilation as a diagnostic tool, to explore and develop methodology to assimilate data in the presence of threshold processes (such as those related to the water cycle), and to develop, implement and evaluate these methods for practical application.

_AIM (Aerosols and Indian monsoons)_

The objective of AIM is to study the impact of aerosols (especially sulphate) on monsoon and tropical climate. The principal goals of the project are to set up a reliable inventory of sulphur dioxide and submicron particle emissions from India, and to model aerosol transport and chemistry over India and the Indian Ocean.

_FOXES (FOrecasting eXtreme Events)_

The FOXES project aims to improve our understanding of the genesis and evolution of extreme events, such as the heavy rainfall events associated with cyclones and depressions from an atmospheric standpoint, as well as their consequences on land surface conditions.

understanding to better harmonize with them. G. Prathap, in his welcome address highlighted the early and significant contributions of the French scientists to issues like global warming. T. S. Prahlad, in his presidential address, emphasized the need for a focused and coordinated effort to address critical issues for societal benefits. S. Elmaleh, Attache for Science and Technology, Embassy of France in India, also participated in the Workshop. Robert Sadourny and P. Goswami highlighted the proposed structure and activities of IFCSER, as well as its achievements so far.

The Workshop then moved onto a discussion and evaluation of various scientific activities in the past year. Philippe Bousquet described the advances under CaFICA and R. Sadourny described the LMD-Z GCM, which is a versatile model, modular, flexible and user-friendly. He elaborated the capability of new generation zoom for monsoon studies. The resolution and parameters involved in the zoom were discussed.

J. Vialard focused on climatic variability and the role of the ocean. He used tools like OPA model, ocean-atmosphere coupled simulations, observational datasets and re-analyses and 4D-variable analysis derived from OPA model. A proposal to study the role of salinity in climatic variability of the Indian Ocean, role of oceanic long waves, mechanisms of ocean dipole and TISO and their interactions with ENSO was made.

J. P. Duvel (LMD) talked about scale interaction over the Indian Ocean. He discussed the LOTI project and VASCO experiments. The LOTI project aims to determine the scale interactions between the ISO and the inter-annual variations of the Indian Ocean basin. VASCO experiments aim to document perturbations of the planetary boundary layer and other ocean-mixed layers by the connective and dynamic systems associated with ISO.

Pierre Soler (LODYC) talked about the marine productivity in the Indian Ocean. He touched upon the main factors which control the marine productivity (intra-seasonal and inter-annual), limiting processes of marine productivity and their space and time distribution, and their impact on phytoplankton species succession. He also talked about the space and time evolution of the fish habitats and forage for important species.

Joydev Chattopadhyay (ISI, Kolkata) talked about mathematical and stochastic modelling and field observations. He also covered marine plankton allelpopathy, field observations, documentation of planktonic bio-diversity and surveillance of bio-diversity.

M. K. Sharada (C-MMACS) talked about mathematical modelling of the marine ecosystem for the Indian Ocean region, with emphasis on 7-component ecosystem model for fisheries aspect.
D. V. Bhaskar Rao (Andhra University, Visakhapatnam) presented some results and a work plan on the study of mesoscale convection over the Indian region, using a high-resolution mesoscale model. He proposed to use the NCAR-MM5 model to simulate the mesoscale features of monsoon circulation, which are not predicted very well using AGCMs with 1° × 1° resolution.

S. Das (NCMRWF, New Delhi) talked about the performance of different cumulus convection schemes in the medium-range weather forecast over India. He brought out the relatively better performance of SAS compared to RAS and KUO statistical methods. However, RAS produced better forecast of the genesis, while tracks of monsoon low/depression were predicted better by SAS.

Mohan Kumar (CUSAT, Kochi) emphasized the non-availability of a comprehensive description of ISM’s intra-seasonal characteristics in terms of the origin, dynamics and three-dimensional heating relationship with other other global circulation features.

P. V. Joseph (CUSAT, Kochi), in his presentation on tropical (monsoon) biennial oscillation and the Asia Pacific wave-analysis and modelling, put forth a proposal to examine these oscillations with GCM experiments.

J. Polcher (LMD) described a new GLSM model, ORCHIDEE. He pointed out the possibility to use this as an impact model and also to study the role of vegetation dynamics in climatic variability, impact of natural and artificial irrigation in tropical areas and the evolution of vegetation as a carbon sink in a changed climate.

K. J. Ramesh (NCMRWF, New Delhi) presented his ideas on predicting the Asian summer monsoon with Megha Tropiques data. The project aims to examine the sensitivity of GCMs in NCMRWF in India and CINES/CNRM, France and also aims to enhance the ability of GCMs in the prediction of Asian summer monsoon in real-time.

Olivier Talagrand (LMD) touched upon the VAMOS project. He described some results obtained from collaborative research between C-MMACS and LMD under VAMOS.

U. C. Mohanty (IIT, New Delhi) discussed the problems associated with simulation LICOS. He emphasized the need to study the feedback of boundary layer and air–sea fluxes in triggering convection, and the role of LSP, surface heterogeneity and orographic effects in simulation of heavy rainfall.

K. Laval (LMD) discussed the simulation of monsoon disturbances in LMD GCM. A 10-year control experiment with LMD GCM has been set-up with orography, to study the simulation of monsoon disturbances. Objective analysis is able to identify minimum of the chosen field to follow the track of the depressions and compute the statistics of the tracks.

B. N. Goswami (CAOS, IISc) described some of the results on analysis of intra-seasonal oscillations. R. Nanjundaiah (CAOS, IISc) described the modelling of hydrological processes in a GCM and impact analysis.

\[ \text{Figure 1. Schematic organization of IFCER science plan and its interfacing.} \]

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New perspectives in cancer diagnosis and treatment by gene profiling

Cancers are caused by a variety of genetic alterations. Mutations in oncogenes or tumour suppressor genes represent the primary genetic lesions – their activation and inactivation, respectively, trigger carcinogenesis. A large number of mutational events and altered programme of gene expression, however, set in when primary tumours evolve to their final malignant state. In colorectal cancers, for instance, mutations leading to inactivation of adenomatous polyposis coli (APC) tumour-suppressor triggers cancerous transformations, resulting in constitutive expression of downstream genes which are involved in the control of cell proliferation and apoptosis. During these early stages of progression, colorectal cancers display chromosomal instability and aneuploidy and sometimes overexpress Csk (COOH-terminal Src tyrosine kinase). Csk in turn down-regulates cSrc (cytoplasmic tyrosine kinase) which regulates cell proliferation. Csk and cSrc thus serve as markers for identification of early polyps. Metastatic colorectal cancers often display mutation in the p53 tumour-suppressor gene which controls programmed cell death or apoptosis. Tumour evolution is thus marked by recruitment of a large number of genes that facilitate its malignant transformation (Box 1). Therapeutic strategies for different tumours can be designed if their abnormally expressed markers are first identified.

Markers apart, the cancerous cells usually exhibit characteristic cyto-pathology. In fact, as a most general practice, microscopic analysis of the tumour sections dominates the world of cancer diagnosis. Cytological classifications of tumours are, however, not without pitfalls. Consider the example of basal cell carcinoma (BCC), which frequently displays mutation in the p53 gene. In an experimental mouse model, carcinoma with remarkable cytological resemblance to BCC can be induced by over-expression of GLI-1 oncogene. These GLI-1-induced carcinoma in mice displayed markers like K5 (keratin5), as in BCCs of man. However, unlike the latter this experimentally-induced BCC in mice did not display any p53 mutation, a hallmark of BCC. This observation calls for a cautious approach in cancer classification and appreciation of the caveat that cyto-pathology is a gross indicator of the underlying cause and that even similar types of cancers can display distinct set of molecular markers. A substantial improvement in the current level of cancer diagnosis and treatment would demand that cyto-pathology be supported by extensive molecular analysis of markers which have gone awry in the cancerous cell types. Indeed, understanding the latter aspect of a cancerous growth, namely, the multitude of genetic alterations involved in cancerous transformation, could hold the key to cancer diagnosis and treatment.

Take, for instance, the case of diffused large B-cell lymphoma (DLBCL). Amongst patients displaying comparable clinical presentations and cytology, only about 40% attain complete remission, the rest succumb. Could this variable response to therapy be due to an underlying difference in the genetic alterations in the DLBCL of the two groups of patients? Addressing questions of this magnitude is a daunting task, when one considers the available compendium of a hundred genes implicated in cancer. Answers to these questions thus cannot be readily discerned by compiling the differences in the pattern of expression of a few genes at a time. Instead, it calls for an entirely different approach where difference between normal and tumourous tissue, in terms of expression of the total complement of the genome, is investigated at once. One of these approaches in genomic sciences, which is in the process of revolutionizing
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Box 2.

Microarrays are glass slides carrying individual signatures of as many as 10,000 genes or more which can be hybridized to their complementary sequences. cDNA microarrays have gene-specific poly-nucleotides (0.6–2.4 kb) robotically spotted on the matrix. For profiling gene expression of tumourous tissue, RNA from tumours as well as normal tissue are first extracted, which serves as a template for cDNA synthesis during which fluorescent tags are introduced. As seen from the figure, cDNA from tumours is labelled red (e.g. Cys3) and that from the normal tissue is tagged with a green label (e.g. Cye5). The mixture of these labelled molecules is used for hybridization of the microarray. Laser scanning and software analysis quantitates this differential binding. RNA over-expressed in tumourous tissue appear as red spots on the matrix, while those expressed in normal tissue but under-expressed in tumours appear green. Genes that are expressed equally in both tumourous and normal tissues display an orange fluorescence.

Genes over- and under-expressed in tumours are potential markers of clinical value which may be used for tumour diagnosis, prognosis, therapy and drug discovery.

DLBCL had 76% survivors, compared to 16% in those with the activated B-cell DLBCL category. Improved precision in therapy apart, in the immediate future, this study should then provide a means for predicting accurately prognosis of patients suffering from DLBCL.

Could all types of cancers be classified using this technique? Extensive investigations undertaken by the National Cancer Institute (NCI), Bethesda over the past several years under its Developmental Therapeutic Programme, is poised to comprehensively answer these questions. In one of its investigations, 60 cancer cell lines derived from tumours from a variety of tissues and organs were typed for the expression of around 8000 genes. Molecular profiling of the transcriptomes of these cell lines and subsequent computational analysis led to the identification of molecular signatures for cancer categories like leukaemia, CNS, colon, renal and ovarian tissues were identified. These signatures could find a huge potential in cancer diagnosis.

A nagging question, however, persists. Would it all be practical to check for the large number of molecular signatures every time an oncologist is faced with the problem of tumour classification? The sheer cost and the magnitude of such analyses could thus hinder their widespread applications. The scenario, however, does not appear as bleak. Take for instance, the case of classification of acute lymphoblastic lymphoma (ALL), and acute myeloid lymphoma (AML). Expression profile of 6817 genes when compared in 27 ALL and 11 AML lines, revealed about 1100 genes which expressed in a manner distinctive of one form or the other of lymphoma. While this appears an intimidating number of genes to be compared among various cancer types, the good news is that of these huge numbers, expression profile of only about 50 markers sufficed for the correct classification of 29 out of 34 randomly selected ALL and AML leukaemia samples! The huge efforts of the consortium, as undertaken by the NCI programme, in compiling the expression of profiles in the different cancer types, therefore, most useful, if these studies can narrow down the number of markers required for highly accurate diagnosis of different categories of tumours.

What promise do these tumour-specific markers hold in designing new therapy? This point has been well-illustrated in

our understanding of genetic basis of carcinogenesis, is the technique of examining expression of hundreds of genes in tiny chips called microarray (Box 2).

In a clever application of this technique of molecular profiling, Alizadeh et al. addressed the questions of unpredictable prognosis of patients suffering from DLBCL. Using microarray technique, they made a comparison of the pattern of expression of a staggering number of genes (around 17,856) from 42 patients suffering from DLBCL. This study led to a broad classification of the DLBCL’s into two distinct categories: one displaying expression profiles comparable to those of the germinal centre B-cell and the other exhibiting the characteristics of activated B-cells. The former showed characteristic up-regulation of a number of genes, notably, those coding for cell-surface proteins CD10 and CD38, nuclear factor A-myb, LMO2 an inhibitor of B-cell proliferation and BCL-6, which is implicated in development of the germinal center. In contrast, the activated B-like DLBCL displayed its own unique signature genes like IRF4, which is involved in B-cell proliferation and genes which block apoptosis including FLIP and BCL-2. In short, gene expression profiling uncovered several distinct categories of markers within what was previously classified as a single type of cancer. The most remarkable aspect of this classification of DLBCL, however, was revealed when the prognosis of patients of these two categories of DLBCLs was compared. Patients with the germinal centre-like