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Computerization of Virus Data and Its Usefulness in Virus Classification

A. S. Kolaskar
P. S. Naik

Bioinformatics,
Distributed Information Centre,
University of Poona, Pune, India

Key Words
Virus data
Data coding
Numerical taxonomy

Summary
Data on 537 Arboviruses and 180 other viruses have been collected and coded in two different formats. These data include information not only regarding the taxonomy and history of isolation, but also regarding the properties of biomacromolecules, proteins and nucleic acids. Information on antigenic relationships, histopathology and experimental viremia is also included. This information is stored in formats which allow the manipulation and analysis of data by dBASE III PLUS and MICRO-IS. A set of programs was written for interconversion and editing purposes. Transmission electron micrographs are scanned and stored. This stored information can be used in viral classification as shown by carrying out analysis of data on the Bunyaviridae family.

Introduction

In recent years advancements in techniques of protein sequencing, nucleic acid sequencing and hybridoma technology have been used by molecular virologists to gain insight into the structure and behavior of viruses. Information generated through such a set of experiments is large and requires storage in a computer-readable form so that access can be gained and the data analyzed. A large number of molecular and epidemiological studies have also been carried out to understand and model the outbreaks of epidemics at the vector and host level. Such modelling studies will have little predictive value if the data on molecular, vector, natural and experimental hosts and from cell culture studies are not used for analysis, suggesting a need for computerization of virus data.

Some of the important groups who organize virus data include: (i) the International Committee on Taxonomy of Viruses (ICTV) [1–3]; (ii) the International Catalogue of Arboviruses [4]; (iii) WHO Center for Collection and Evaluation of Data on Comparative Virology in Munich [personal commun.], and (iv) Virus Data Exchange (VIDE) project of the Australian National University [personal commun.].

To complement these efforts and to aid virologists, molecular biologists, clinical personnel,

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A.S. Kolaskar
Bioinformatics, Distributed Information Centre
Department of Zoology
University of Poona, Pune 411007 (India)

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epidemiologists, and industrial users, we have initiated the computerization of data on animal viruses. In the first phase of this project, information on arboviruses has been computerized. An open-ended numerical coding system, pictorial data storage and standardization of vocabulary are some of the features of the data bank which are discussed in the following sections. It is pointed out that this data bank can be used as an aid to classify viruses objectively. At present, information on 537 arboviruses has been coded and is available in computer-readable form. Information on another 180 viruses is also computerized.

Table 1. Categories incorporated for coding data in dBASE III PLUS format

1 Virus status and distribution
2 The original source of the virus
3 Method of isolation and validity
4 Physicochemical properties of virus
5 Stability of infectivity and virulence
6 Virion morphology
7 Morphogenesis
8 Hemagglutination
9 Antigenic relationship
10 Susceptibility of cell systems
11 Natural host range
12 Experimental viremia
13 Histopathology
14 Human disease
15 Links with other data banks
16 References

Coding of Virus Data in dBASE III PLUS

Information on viruses has been coded using the dBASE III PLUS data base management system [5, 6]. The format chosen allows the user to extract all or part of the information on a particular virus. Information is stored under 16 different categories which are listed in table 1. There are several subcategories and they vary in number and organization. In order to extract information based on the properties of viruses, it is essential to make use of a controlled vocabulary during coding and querying. A controlled vocabulary is essential since the information developer also uses synonyms and acronyms in the report. Examples of some of the controlled vocabulary terms are given in table 2. We have developed a dictionary of

Table 2. Words and their possible synonyms incorporated in the data bank

A single word and its possible synonyms
Idoxuridine: 5-iodo-2-deoxyuridine, Dendrid, Herpid, Kerecid, Stoxil
Idoxuridine = An antiviral agent
5-iodo-2-deoxyuridine = The chemical name of idoxuridine
Dendrid = Trade name of idoxuridine eye drops
Kerecid = Trade name of idoxuridine eye drops
Herpid = Trade name of 5% idoxuridine
An acronym and its full form
SAM = S-Adenosyl-*L*-methionine
SAM = An intracellular carrier and donor of activated methyl groups
A virus and its possible synonyms
Japanese encephalitis virus = Japanese B virus, Russian autumn encephalitis virus
An arthropod and its possible synonyms
Culex quinquefasciatus = Culex fatigans, Culex (Culex) fatigans, C. fatigans

Fig. 1. A sample dBASE data file for Japanese encephalitis virus.

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VIRUS STATUS AND DISTRIBUTION
  Accession no. : A0195-000
  Virus name, prototype : Japanese Encephalitis
                          (Nakayama)
  Abbreviation : JBE
  Antigenic group : B
  Arbovirus status : ARBOVIRUS
  Family : FLAVIVIRIDAE
  Genus : FLAVIVIRUS
  Taxonomic status : FLAVIVIRUS
  Biosafety level (SALS rating) : 3
  Geographical distribution :
          1) INDIA
          2) JAPAN
          3) JAVA
          4) KOREA
          5) NORTH AND S.E. ASIA
          6) NORTHEASTERN ASIA
          7) TAIWAN
          8) THAILAND

ORIGINAL SOURCE OF THE VIRUS
The original source of the virus was isolated by :
      T.Mitamura and M.Kitaoka, et al.
The place of isolation of the original source was:
      Tokyo,
The country of isolation of the original source
was : Japan
The animal from which the original source was
isolated : MAN
The age of the source animal is : 19 YEARS
The sex of the source animal is : male
The virus was isolated from the sample : BRAIN
The signs of illness during original isolation
were : ENCEPHALITIS
The sample collection date is (D/M/Y) : 21/08/1935
The sample collection method is : AUTOPSY
The sample collection place is :
HOSPITAL IN TOKYO, JAPAN
The macrohabitat is : URBAN
Method of storage until inoculated : NO STORAGE
METHOD OF ISOLATION AND VALIDITY
Inoculation date is (D/M/Y) : 21/08/35
The animal inoculated : WN MICE
The route of inoculation is : INTRACEREBRAL
Reisolation of the virus was attempted.
Homologous antibodies were not produced by source
animal.
Tests used : NT

PHYSICOCHEMICAL PROPERTIES
The virus is an RNA virus
The virus is not a DNA virus
The virus is a single stranded virus
The virus is not a double stranded virus
No. of pieces of the genome are 1
Number of virion polypeptides 3
Details of virion polypeptides
     9,000-10,000 (MEMBRANE POLYPEPTIDE),
     13,000-15,000 MW (CAPSID POLYPEPTIDE)
Virion density in (gm/cm-cube) 1.19
Virion density measured in SUCROSE
Virion sedimentation coefficient (in s) 200
Nucleocapsid density (in gm/cm-cube) 1.31
Nucleocapsid density measured in SUCROSE

STABILITY OF INFECTIVITY AND VIRULENCE
  Effect of ether : yes
  Effect of chloroform : not known
  Effect of deoxycholate : yes

VIRION MORPHOLOGY
  Shape of the virus is : SPHERICAL
  Dimensions of the virus : 48.6-57.6 nm
  Method of measurement : EM
  Nature of envelope/surface projections : SPIKES
  Nucleocapsid dimensions : 27.3-32.3 nm

MORPHOGENESIS
  Site of virion assembly in cell :
      CYTOPLASM
  Site of virion accumulation in cell :
      CYTOPLASM VACUOLUM

HEMAGGLUTINATION
 Hemagglutination was observed
 Antigenic source for testing hemagglutination :
     SMB.EXT.BY BORATE-KCl, pH 9.0; ACETONE-ETHER;
     SUCROSE-ACETON
 Erythrocytes used for hemagglutination : GOOSE
 Minimum pH for hemagglutination : 6.0
 Maximum pH for hemagglutination : 7.2
 Optimum pH for hemagglutination : 6.6
 Minimum temperature for hemagglutination : 4 degC
 Maximum temperature for hemagglutination : 37 degC
 Optimum temperature for hemagglutination : 25 degC
 Serological methods recommended : HI, CF, NT

ANTIGENIC RELATIONSHIP

     Related antigenically to other flaviviruses
     (Group B)
     Viruses antigenically related : West Nile,
     Murrey Valley Encephalitis, Saint Louis
     Encephalitis.

SUSCEPTIBILITY OF CELL SYSTEMS
    Cell type         1) CHICK EMBRYO
        Cell line or prim.cul.: PC
        CPE Observed : YES
        Plaque observed : YES
        Day Plaque observed : 5
    Cell type         2) HUMAN EPITHELIAL
        Cell line or prim.cul.: CL
        CPE Observed : NO
        Plaque observed : NOT KNOWN
    Cell type         3) L MOUSE CELLS
        Cell line or prim.cul.:
        CPE Observed : NO
        Plaque observed : NOT KNOWN
    Cell type         4) VERO
        Cell line or prim.cul.: CL
        Virus passage history : P-52
        CPE Observed : NOT KNOWN
        Plaque observed : YES
        Day Plaque observed : 4
        Size of Plaques : 3.0 mm
        Titer (Plaque) : 9.1 (PFU/ml)
    Cell type         5) LLC-MK2
        Cell line or prim.cul.: CL
        CPE Observed : NOT KNOWN
        Plaque observed : YES
        Day Plaque observed : 3
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Fig. 1. cont. on p. 136

Fig. 1. cont., for legend see p. 135

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        Size of Plaques : 8.0 mm
        Titer (Plaque) : 9.4 (PFU/ml)
    Cell type          6) C6/36
        Cell line or prim.cul.: CL
        CPE Observed : NOT KNOWN
        Plaque observed : YES
    Cell type          7) PS
        Cell line or prim.cul.: CL
        Virus passage history : P-43
        CPE Observed : YES
        Day CPE observed : 3
        Extent of CPE : 100 %
        Titer (CPE) : 8.0 TCD50/ml
        Plaque observed : YES
        Day Plaque observed : 3
        Size of Plaques : 5.0 mm
        Titer (Plaque) : 8.3 (PFU/ml)

NATURAL HOST RANGE

  Species : ANOPHELES BARBIROSTRIS
  No. of isolations : 1

  Species : CULEX TRITAENIORHYNCHUS
  Country from which species collected : INDIA
  No. of isolations : 1

  Species : ANOPHELES HYRCANUS
  Country from which species collected : INDIA
  No. of isolations : 1

  Species : MAN
  Country from which species collected : INDIA
  No. of isolations : MANY

  Species : CULEX PSEUDOVISHNUI
  Country from which species collected : INDIA
  No. of isolations : 1

  Species : CULEX FUSCOCEPHALA
  Country from which species collected : INDIA
  No. of isolations : 1

  Species : HORSES
  Country from which species collected : JAPAN
  No. of isolations : MANY

  Species : BIRDS
  Country from which species collected : JAPAN
  No. of isolations : MANY

  Species : CULEX PIPIENS
  Country from which species collected : JAPAN

  Species : CULEX GELIDUS
  Country from which species collected : JAPAN

  Species : CULEX VISHNUI
  Country from which species collected : JAPAN
  No. of isolations : 1

  Species : MAN
  Country from which species collected : JAPAN
  No. of isolations : MANY

  Species : CX.TRITAENIORHYNCHUS
  Country from which species collected : JAVA
  No. of isolations : 3

  Species : POIKILOTHERMIC HOSTS
  Country from which species collected : KOREA

  Species : CX.PIPIENS
  Country from which species collected : NORTH AND
  S.E. ASIA

  Species : CX.TRITAENIORHYNCHUS
  Country from which species collected :
  NORTHEASTERN ASIA
  No. of isolations : MANY

  Species : CX.GELIDUS
  Country from which species collected : S.E. ASIA

  Species : CX.ANNULUS
  Country from which species collected : TAIWAN

  Species : BATS
  Country from which species collected : TAIWAN

  Species : POIKILOTHERMIC HOSTS
  Country from which species collected : TAIWAN

  Species : CX.FUSCOCEPHALA
  Country from which species collected : THAILAND

EXPERIMENTAL VIREMIA

        1) Experimental animal used : MICE
          Age of the animal : NB
          Route of inoculation : IC
          Inoculation dose : 0.01
          Evidence of infection : DEATH
          Average Survival Time (days) from : 3
          Average Survival Time (days) upto : 4
          Titer (log10/ml) : 8.0

        2) Experimental animal used : MICE
          Age of the animal : NB
          Route of inoculation : IP
          Inoculation dose : 0.01
          Evidence of infection : DEATH
          Average Survival Time (days) from : 4
          Average Survival Time (days) upto : 5
          Titer (log10/ml) : 8.0

        3) Experimental animal used : MICE
          Age of the animal : WN
          Route of inoculation : IC
          Inoculation dose : 0.03
          Evidence of infection : DEATH
          Average Survival Time (days) from : 5
          Average Survival Time (days) upto : 6
          Titer (log10/ml) : 7.0

        4) Experimental animal used : MICE
          Age of the animal : WN
          Route of inoculation : IP
          Inoculation dose : 0.2
          Evidence of infection : DEATH
          Average Survival Time (days) from : 6
          Average Survival Time (days) upto : 10
          Titer (log10/ml) : 1.0
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Fig. 1. cont., for legend see p. 135

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          5) Experimental animal used : MONKEYS
             Route of inoculation : IC
             Inoculation dose : 0.2
             Evidence of infection : DEATH

          6) Experimental animal used : HAMSTER
             Route of inoculation : IC
             Evidence of infection : DEATH

          7) Experimental animal used : GUINEA PIG
             Route of inoculation : IC
             Evidence of infection : VIREMIA

          8) Experimental animal used : RABBIT
             Route of inoculation : IC
             Evidence of infection : VIREMIA

          9) Experimental animal used : CHICK
             Route of inoculation : IC
             Evidence of infection : VIREMIA

         10) Experimental animal used : HORSES
             Route of inoculation : SC
             Evidence of infection : VIREMIA

         11) Experimental animal used : BATS
             Route of inoculation : SC
             Evidence of infection : VIREMIA

         12) Experimental animal used :
             EMBRYONATED EGGS
             Route of inoculation : YS
             Evidence of infection : DEATH

HISTOPATHOLOGY
  Animal on which lesions observed and characters
  of lesions :
         1) MAN :
            ENCEPHALITIS
         2) Animal not defined :
            ACUTE ENCEPHALITIS
  Organs and tissues effected in animal :
         1) Animal not defined :
            BRAIN
         2) MAMMAL :
            BRAIN
         3) LOWER VERTEBRATES :
            BRAIN
  Category of tropism in animal :
         1) Animal not defined :
            NEUROTROPIC, ENCEPHALITIS

HUMAN DISEASE
  Human disease in nature is significant
  Human disease leading to death is significant
  Human disease is significantly residual
  Laboratory infection is reported to be
  subclinical
  Laboratory infection is reported to be an overt
  disease
  Clinical manifestations :
       FEVER
       HEADACHE
       PROSTRATION
       STIFF NECK
       CNS SIGNS
       ENCEPHALITIS
       CNS PLEOCYTOSIS
  Category of human disease :
       ENCEPHALITIS

LINKS WITH OTHER DATA BANKS

ID CODE as in EMBL :
M62934; M18370; M55506; M73710; D00037; N00037;
D90195; M14933; M15337; M16574; D90194;

ID CODE as in GENBANK :
M62934; M14933; M15337; M18370; M55506; M73710;
M16574; D90195; D90194; D00037; N00037;

ID CODE as in NBRF :
A27403\ A26465; A27844;

ID CODE as in HDB :
1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922;
1923; 1924; 1925; 1926; 1927; 1928; 1929; 1939;
1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938;
1939;

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synonyms and acronyms. At present 1,400 words are included in this dictionary. We are also making use of those controlled vocabulary terms which are already used by hybridoma data bank developers [7] and protein sequence data bank developers [8]. A sample dBASE data file for the Japanese encephalitis virus of Flaviviridae family is given in figure 1. It can be seen from figure 1 that we have not fed sequences of either nucleic acids or proteins of the virus, but pointers are available through accession numbers given in EMBL nucleotide sequence data banks and Genbank for nucleic acid sequences. Protein sequence information can be obtained using NBRF-PIR accession numbers. Information on the 3D structure of the proteins can also be obtained from the Protein Data Bank because in the NBRF PIR sequence data bank there is a field which indicates whether 3D data are available in the Protein Data Bank of Brookhaven National Laboratory in the USA. Information regarding monoclonals and hybridomas is not fed into our data bank but accession numbers in the Hybridoma Data Bank (HDB) of IUIS-CODATA are provided. It may be pointed out that HDB is available on Microbial Strain Data Network (MSDN) through Telecom Gold in the UK and Dialcom in the USA. The protein and nucleic acid sequence data banks are also available online through various USA and European networks. Thus, wherever possible pointers to gain access to computerized data are provided.

Pictorial Data Storage

Many times in biology, pictorial information reveals important features which are difficult to point out by coding the information in the alpha-numeric form. Electron microscopic pictures of biological systems provide very high resolution information regarding the structure and organization at the micro level. This is particularly true for transmission electron micrographs at high resolution which reveal the morphology of the virus. Several methods in electron microscopy, such as metal shadowing, negative staining and freeze fracture, have been employed to study the structure of viruses [9]. The three-dimensional structures of viruses can be produced using computer analysis and can also be determined by fast Fourier reconstruction [10]. We have therefore stored transmission electron micrograph images of viruses on the computer in the TIFF format.

Development of Numerical Codes

The hard data on viruses can be divided into two parts: attributes, and measurable quantities. Comparison of the measurable quantities is possible if the input data are standardized and then coded. In order to achieve this we have developed a new numerical code to describe virus properties. Our data on viruses were divided into three main categories: (a) binary; (b) numeric, and (c) character information, as has been done in the RKC codes for microbes [11]. The codes for some of the virus properties are given in table 3. Data coding on the size of virus, virion morphology, etc., is carried out by using codes which support numeric data, while the information on the history and distribution of the viruses is coded using codes which support character data. The coding system is open ended and makes it possible to update and add new codes from time to time. The addition of new codes does not alter the structure of the data bank. This is mainly because we have distinguished between the experiments giving negative results and experiments not carried out to check the properties.

The coded information is entered in the computer to form a flat file having a large

Table 3. RKC-like codes for some of the virus properties

Codes of binary data
007564 Storage of the virus after isolation is at room temperature (25°)
007565 Storage of the virus after isolation is from 4° to room temperature (25°)
007566 Storage of the virus after isolation at 4°
007567 Storage of the virus after isolation from –20 to 4°
007568 Storage of the virus after isolation at –20°
007569 Storage of the virus after isolation from –20 to –70°
007570 Storage of the virus after isolation at –70°
014201 Type of nucleic acid is DNA
014202 Type of nucleic acid is RNA
014203 Strandedness of nucleic acid is single
014204 Strandedness of nucleic acid is double
014205 Polarity of the nucleic acid is positive
014206 Polarity of the nucleic acid is negative
020201 Mode of transmission of the virus is vertical
020202 Mode of transmission of the virus is horizontal
020203 Mode of transmission of the virus is mechanical
Codes for numeric data
532101 Molecular weight of the entire genome
532103 Percentage weight of the nucleic acid
532106 Percentage composition of base A in entire genome
532107 Percentage composition of base T in entire genome
532108 Percentage composition of base G in entire genome
532109 Percentage composition of base C in entire genome
532110 Percentage composition of base U in entire genome
532315 Percentage weight of the lipids
542101 Virion density in grams per cubic centimeter
542102 Virion sedimentation coefficient in S
Codes for character data:
c07415 Place of collection of the animal from which virus was first isolated
c07418 Macrohabitat of the place of collection of the animal from which virus was first isolated
c07419 Microhabitat of the place of collection of the animal from which virus was first isolated
c14322 Antigenic group of the virus
c14323 Taxonomic status of the virus

number of fields, each field having variable length. Such a flat file structure is adapted mainly because the data base management system called MICRO-IS, developed at the National Institutes of Health, Bethesda, Md. [12], to carry out analysis of microbial data, can be used.

A set of programs is written which converts properties expressed in words into numerical code. Such a software package to automatically convert the dBASE III PLUS data file into MICRO-IS input format is available.

Identification and Classification of Viruses

An example is given here to classify viruses from the family of Bunyaviridae using the sys-

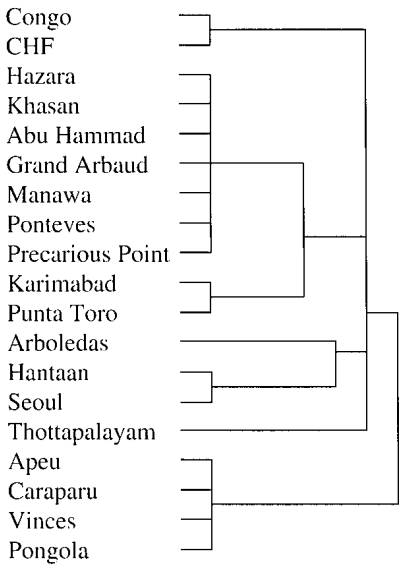

Fig. 2. A possible classification of viruses among the family Bunyaviridae. Nairoviruses, Congo and Crimean hemorrhagic fever (CHF) form one cluster. Nairoviruses, Hazara, Khazan and Abu Hammad, are part of the cluster formed by Uukuvirus, Grand Arbaud, Manawa, Ponteves, and Precarious Point. The Phleboviruses, Karimabad and Punto Toro, are closest to Uukuviruses thus supporting recent conclusions regarding the evolutionary relationship between these two genera [13].

tem. Four properties from 19 randomly chosen members of the Bunyaviridae family are used to create a weight matrix. These are: (i) type of vector; (ii) type of host; (iii) information about the genome, and (iv) results from hemagglutination experiments. Single linkage cluster analysis was carried out using the above-mentioned weight matrix. Results given in figure 2 point out that the weight matrix formed by only the above four properties does give results which are very similar to what we know today about the classification of viruses from the Bunyaviridae family. A better resolution can be achieved if a weight matrix is formed using many properties which are listed in our data bank.

Availability of Data

These virus data are available online to all the MSDN users. Access to MSDN can be gained not only through Telecom Gold and Dialcom but also through Internet. The software being used to gain access to and analyze information is called INFO. The data are actually situated at Base de Dados Tropical, Campinas, Brazil. At present only alphanumeric data are available online. We will also provide a copy of the data base on floppy diskette at nominal handling charges.

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