A study on warning and forecasting system of bird flu and other accidental diseases based on scientific database

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Chinese Academy of Sciences

Outline

- ☐ Background of the project
- Project objectives
- ☐ Achievements update
- ☐ Further steps

Organizations involved

- ☐ Institute of Microbiology, CAS
- ☐ Computer Network Information Center, CAS
- ☐ Institute of Zoology, CAS
- **☐** Wuhan Institute of Virology, CAS
- Qinghaihu National Nature Reserve, Qinghai Prov.

Project objectives

- 1. Development of data standards and metadata
- 2. Integration of avian-flu databases
- 3. Epidemiological and ecological researches
- 4. Bioinformatic platform for avian-flu analysis
- 5. Alarming and predicting system
- 6. Construction of cooperative scientific research network
- 7. Establishment of information publication system

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禽流感项目Porta

欢迎:

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合作单位介绍 ②

含流感项目介绍

∃ i ×

禽流感(Avian Influenza,AI)是由正粘病毒科流感病毒属A型流感病毒引起的一种急性、高度接触性的禽类传染病,被世界卫生组织 (OIE)列为A类传染病,我国政府也将其列为一类动物疫病。AI的亚型较多,其中以H5和H7亚型为主的高致病性禽流感(HPAI)危害) 巨大。自1959年以来,全世界共爆发高致病性禽流感40次,90年代后又爆发31次,特别是自2003年底以来,亚洲的韩国和日本相继报主 发了H5N1亚型引起的高致病性禽流感。随后东南亚的越南、泰国、印度尼西亚也先后爆发了H5N1引起的高致病性禽流感,并呈蔓延趋 势。2004年初,我国也宣布已经在广西、湖南、湖北、广东、上海、云南、甘肃、陕西、安徽、浙江等地证实了有高致病性禽流感的发 生。显然,禽流感在世界各地爆发的频率越来越高,流行的面也越来越广。更为严重的是,1997年香港发生H5N1亚型禽流感感染人并引 死亡的事件后, 2003至2004年间相继又有H5N1、H7N7亚型流感病毒感染人并引起死亡的报道。因此,禽流感还与人类的生命健康直: 相关,具有非常重要的公共意义。

|疾病爆发与蔓延的传播途径。以往的研究迹象表明:禽流感病毒的大范围跨越式感染可能与禽鸟等病毒戴体的南北流动有关。我国出现; 流感地区在分布上的散布性,而且禽流感在我国的发生有逐渐北移的趋势,特别一些养鸭场和养鹅场的被感染,都说明其中候鸟迁徙扩[。] 是可能的传播途径。因此推测:候鸟的迁徙与禽流感的大面积爆发与蔓延可能有一定关系。而且,鸟类本身是禽流感病原的自然携带者。 国外研究发现野鸟本身携带有A型病毒。国际学术界普遍认为我国华南地区是禽流感易发地区,并可能为禽流感的疫源地。因为华南地区 网密布、拥有大范围、高密度禽类及哺乳类动物面积,人口稠密、人、猪、家禽和水禽之间接触非常紧密。另外该地气候温暖湿润利于:

由于鸟类具有跨国界的迁徙行为,因此,携带有病原的鸟类常常具有大面积范围甚至全球性感染力。鸟类的迁徙行为也因此是一种可能(

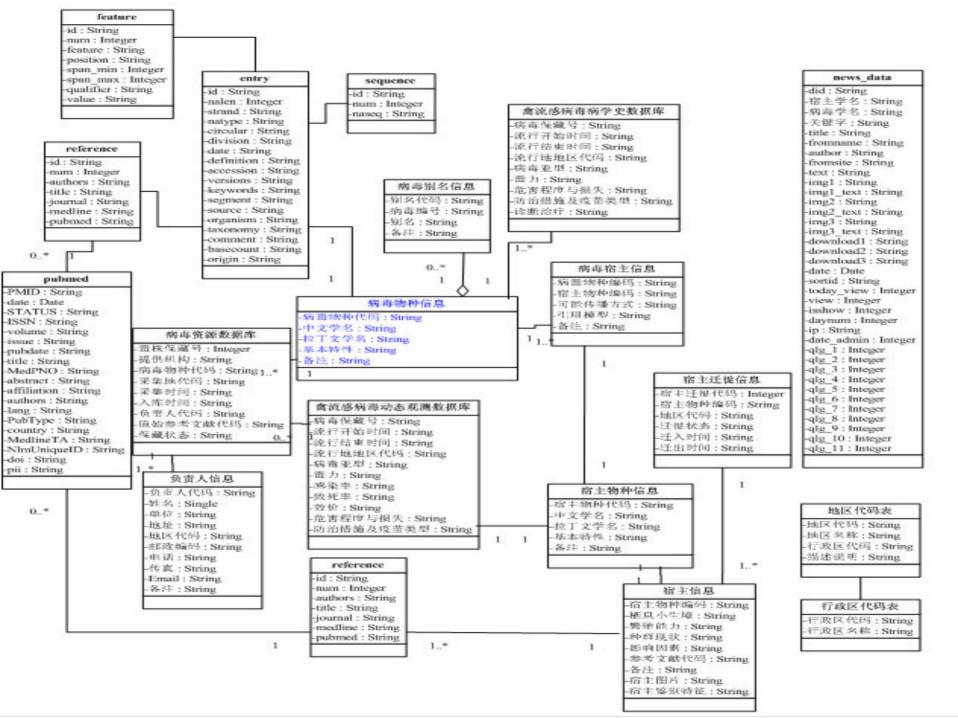
|毒存活,尤其以禽粪喂鱼、水禽放养和鸟类丰富地生产生态模式,正处于国际候鸟迁徙路径线上。这些特点决定了禽流感可通过粪便、: 系、饲料、活禽市场等、以及鸟类迁徙和共同中间宿主等环节按"水禽 — 家禽 — (水禽) — 猪 — 人"之间的交互感染。目前流

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http://birdflu.sdg.ac.cn http://www.avian-flu.cn

Data standards and metadata

- □ Data standards for bird flu basic databases are made under requirements of bird flu basic databases for dynamic monitoring, historic epidemic situation, genetic resources and so on.
- Metadata standards are established and further developed into a descriptive language used for organizing, managing and applying bird flu resources "Data standards for comprehensive information platform and alarming and predicting system of AI epidemic of CAS"



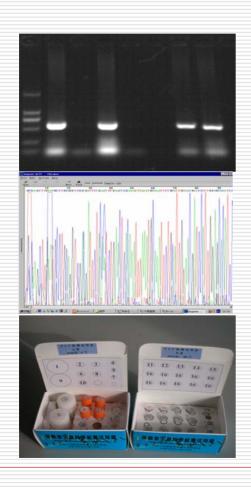
Integration of bird flu databases

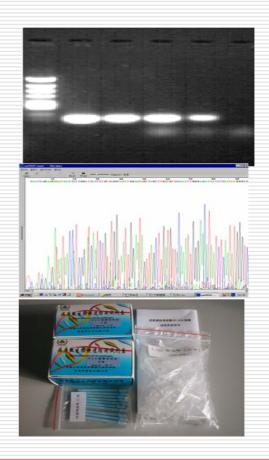
- Anticipated databases
 - viral resource database
 - ② genetic resource database
 - ③ historic epidemic situation database
 - 4 dynamic observations database
 - ⑤ host areas and environmental database
 - 6 scientific literature database
 - nucleotide and protein sequences database
 - ® international cooperation information
- ☐ Other databases during the project (for ongoing experiments)

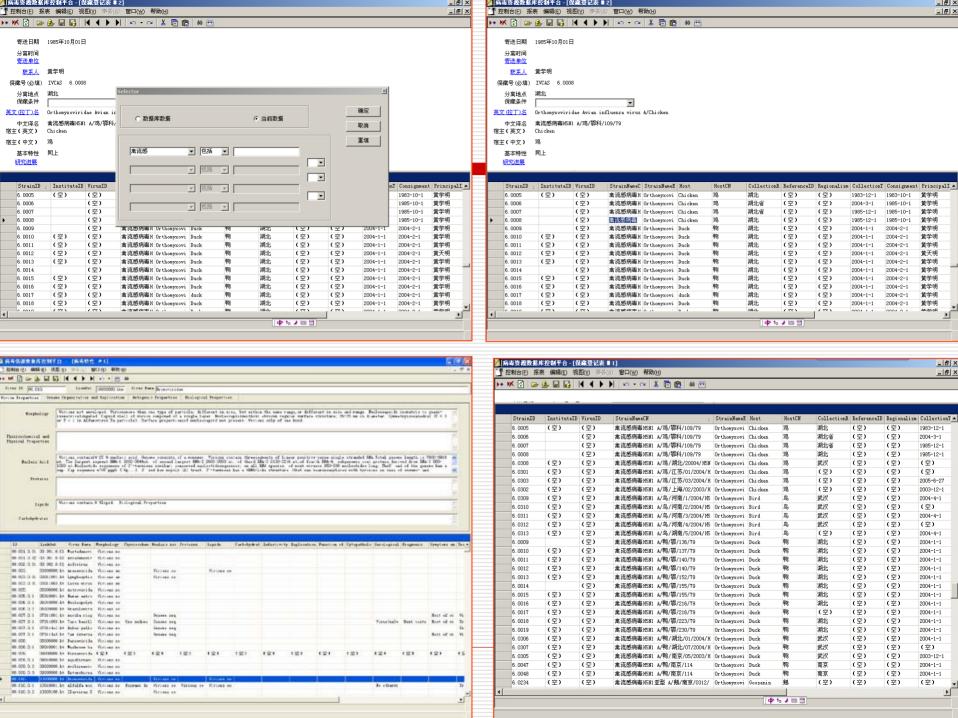
Isolation and identification of virus

- Isolation and identification of virus
- Animal tests
- Sequencing and genetic analysis of virus gene

RT-PCR identification







Data submission form

国流量等突	发疾病综合信息平台与预警预报系统	我的页面
项目介绍 ② 数据规	范 ② 数据录入 ② 数据访问服务 ② 生物信息学分析系统 ② 协同环境 ② 对タ	大发布 ② 成果 ②
宿主物种信息数据录入		B
宿主物种代码	(主健请输入唯一的值)	Data should be
中文学名	宿主物种的中文学名,长度请不要超过50个字符,汉字不超过25个)	submitted in
拉丁文学名	(宿主物种的拉丁文学名,长度请不要超过500个字符,汉字不超过250个)	required form
		⋈
基本特性	(关于宿主物种的基本特性的描述,请不要超过4000个字符,汉字不超过2000个)	^
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备注		
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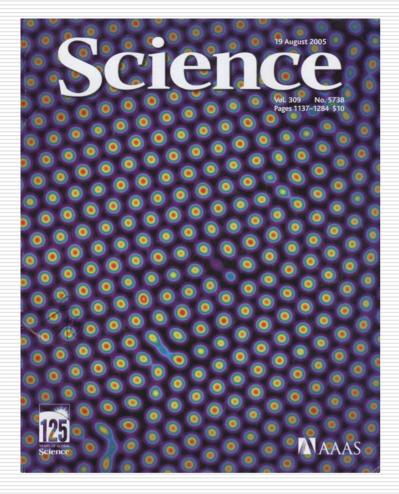
Susceptible hosts / AIV sensitive animals

Great Blackheaded Gull

Bar-headed Goose







BREVIA

Highly Pathogenic H5N1 Influenza Virus Infection in Migratory Birds

J. Liu, ¹a † H. Xiao, ^{2,4}* F. Lei, ²a Q. Zhu, ⁵ K. Qin, ¹ X.-w. Zhang, ⁶ X.-l. Zhang, ¹ D. Zhao, ¹ G. Wang, ^{2,4} Y. Feng, ^{2,4} J. Ma, ² W. Liu, ² J. Wang, ⁶ G. F. Gao²†

Avian influenza virus (AIV) involving at least three subtypes, H5, H7, and H9, has emerged as an important pathogen in the poultry industry and is of major current global health

concern (/). The first case report of chicken to human transmission was in Hong Kong in 1997 (2); since 2008, H5N1, a highly pathogenic AIV, has emerged in 10 Asian countries, including Thailand, Vietnam, and China (Fig. 1), and has claimed at least 53 human lives. Until recently, migratory waterfowl seemed to be exempt from widespread infection, although spondic cases were recorded (3). Here we describe an outbreak of highly pathogenic H5N1 infection among waterfowl in Lake Qinghaihu, Gangcha County, Oinghai Province, in western China (Fig. 1).

On 4 May 2005, a few birds were found dead on Bird Island, and by the end of June more than a thousand birds were affected. This lake is one of the most important breeding loca-

tions for migratory birds that overwinter in Southeast Asia, Tibet, and India (Fig. 1). Several species were infected, including the bar-headed goose (4nur indicus), great black-headed gull (Larus ichthyaetus), and brown-headed gull (Larus brunnicephalus). Two key symptoms were noticed: abnormal reurological signs (tremor and opisthotonus) and diarrhea. Among the gross lesions, pancreatic necrosis was obvious and was confirmed by tissue section where extensive areas of lytic necrosis were seen. consistent with pathology observed in domestic geese and ducks infected with H5N1 AIV (3). Brain sections revealed glial cell infiltration, perivascular cuffing, and consestion in the blood vessels. Serological tests (4) from one bar-headed goose and one brownheaded gall confirmed the presence of hightiter antibody against H5N1 AIV.

and cloaca of sick and dead birds. Four of the isolates from different bird species were com-

Several H5N1 viruses were isolated from the

viscera, busin, and swabs of the oropharynx



Fig. 1. (A) The reported H5N1 AIV prevalence sites during the 2004 outbreak in China are Fig. 1., (A) the reporate n-SNI AV presented in the curring the LOAD colorates in c. in ma are highlighted in yellow (E). A roots indicate the migrating notate of the barhaded good principles to Laie Cinglishia. (B) A sick bar hashed good principles griptical quisited notations before dying. (C) Ear-haded good principles with pin-point near-otic leatons (annow). (D) Microsoptic leatons in bar-hashed good brain, showing congestion in the body deside (white annow) and gist a cell inflammation (Black annow). Hermitopylin and earth x-SS (load bars, 750 µm²).

pletely sequenced (4) and amounted to be closely related. None of the GenBank sequence data for known H5N1 AIV genomes completely matched our sequences, implying the viruses are reassortants. Five of the eight genomic segments (M, PA, PB1, PB2, and NS) were closely related to a Hong Kong 2004 is date (A/peregrine falcon/HK/D0028/04)(3). We observed several characteristics in our four isolates: first, the sequence PQGERRRKKR/G, denoting multiple basic amino acids at the cleavage site of the hemagglutinin; second, a virulence island in the PB2 gene, E627K, first seen in Hong Kong in 1997 (5); and third, a deletion of 20 amino acids in neuromidase (amino acid positions 49 to 69), also associated with high virulence.

To test virulence, mice and chickens were infected with the BhGoose/OH/1/05 (4) isolate.

All eight infected chickens died within 20 hours. and seven of eight infected mice died within 72 hours; the last died 96 hours post-infection. Barlier isolates taken from ducks in China were less vimlent in mice and chickens (6). Hence we speculate that viruses might be emerging from reassortants that originate in birds overwintering in southeast Asia (7).

The occurrence of highly pathogenic H5N1 AIV infection in migrant waterfood indicates that this virus has the potential to be a slobal threat: Lake Qinghaihu is a breeding center for migrant birds that congregate from southeast Asia, Siberia, Australia, and New Zealand.

- References and Notes
 1. R. J. Webby, R. G. Webster,
 Science 202, 1519 (2003).
 2. K. Subbarso et al., Science 279,
 293 (2936).
 3. K. S. Li et al., Neture 430, 209
- K. S. Li *et al.*, *Nature* 439, 209 (2004).
 Materials and methods are available as supporting material on Science Ordins.
 M. Hatta *et al.*, Science 293, 1940 (2001).
 H. Chen *et al.*, *Proc. Natl. Acad. Sci. USA* 103, 10452 (2004).
- T. H. Cheng et al., Nurse Sinio: Avez (Science Press, Beijing, 1979), vol. 2.
- 1970), vol. 2. Andrew Lawrence of the control of th Natural Sciences Foundation of China (grant nos. 30471282 and 30228025). Sequence data derived from this study were de-posited in Gentlank with acces-sion no. DQ 100542-DQ 100573.

Supporting Online Material www.s.denoemag.org/cgi/cont.em/full/1115273/DC1 Meterials and Methods

Published online 6 July 2005;

include this information when diting this paper.

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*These authors contributed equally to this work. †To whom correspondence should be addressed. E-mail: gast@im.ac.or (GF.G); |N@cau.edu.or (JL.)

1206



Tree Sparrow



Great Cormorant



Brown-headed Gull



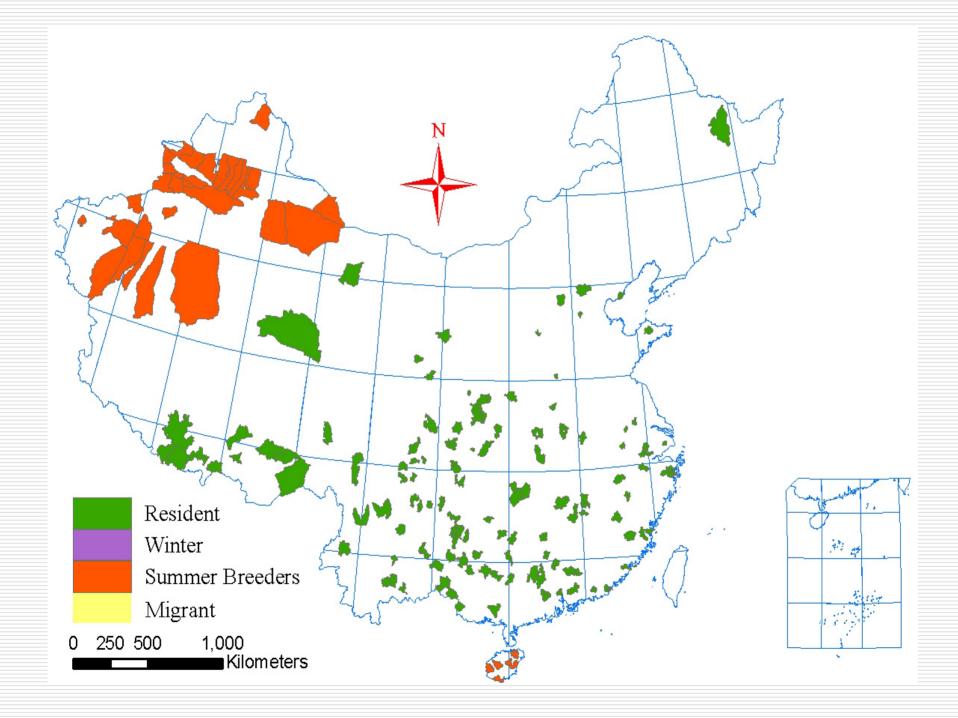
Greater White-fronted Goose



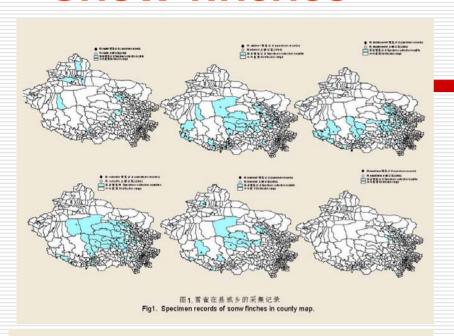


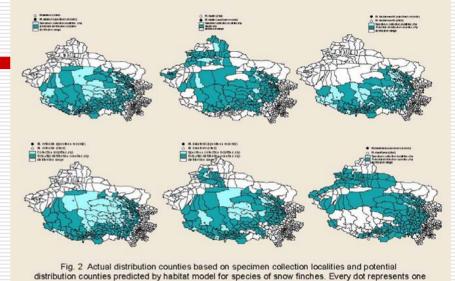


Photo by YZMB F5.61/50



Snow finches

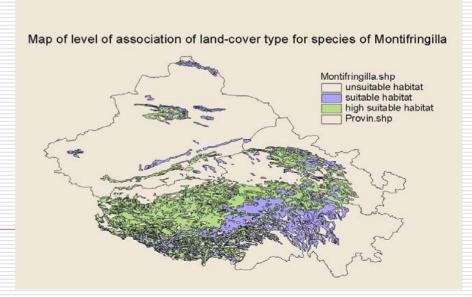




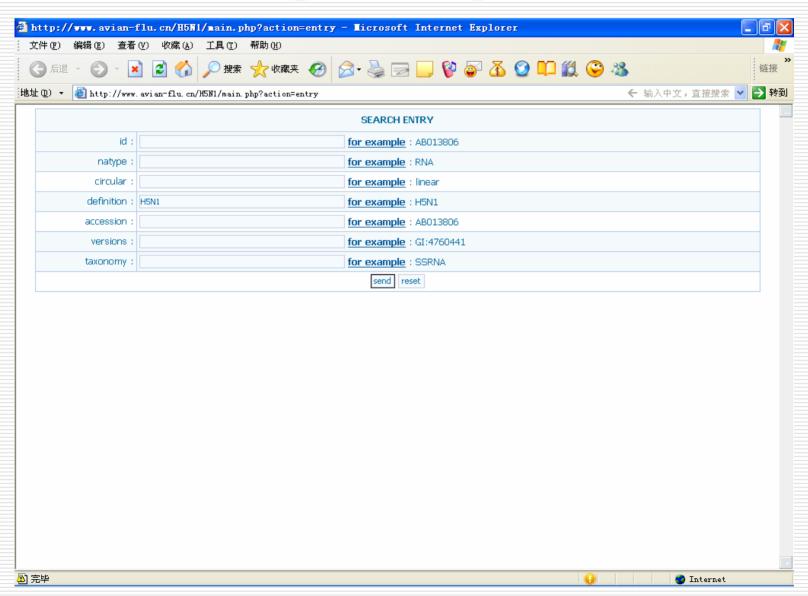
site from which one or more species were collected.

Ruffcolite abp
reside habitat
resid

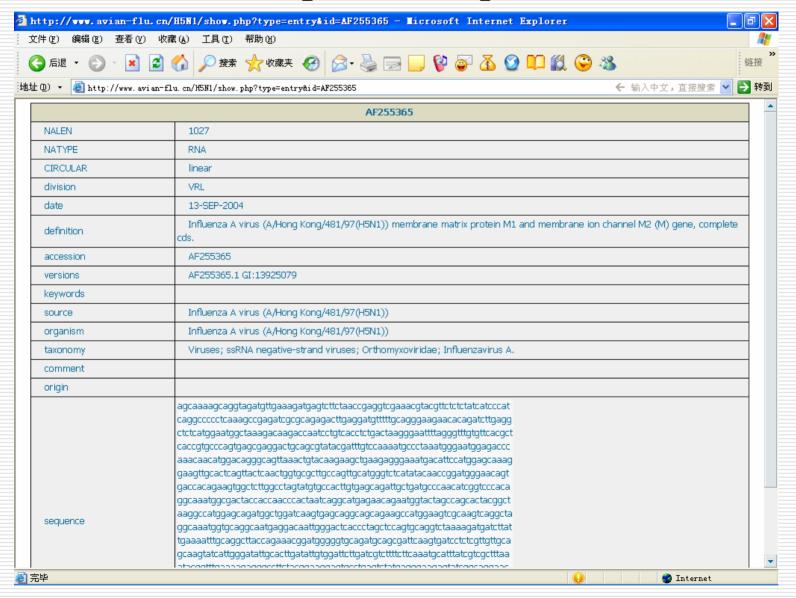
Fig.3 Sutiable habitat of snow finch predicted by WHR model



Nucleotide and protein sequence database



Nucleotide and protein sequence database



☐ Epidemiological researches of avian influenza virus:

Our researches are focus on molecular epidemiology, genomic, proteomic, genetic mutations and pathologic mechanism.

☐ Ecological researches of AI :

We investigate wild birds, domestic poultry and mammals to learn their ecological behavior, pathologic mechanism of virus, animal hosts of HPAI H5N1, allocation of hosts and their ecological characteristics.

Ecology of AI infected sites









(Birds collecting around Lake Qinghai)

Location	Туре	Number	Latitude	Altitude
Gang Cha	Little Owl	1	N36.59' E99.35	3200 (M)
	Hume's Ground pecker	17		
	Horned Lark	15		
	Great Black- headed Gull	11		
	Rock Sparrow	2		
	Bar-headed Goose	1		
	Twite	15		
	small snowfinch	3		
	Lesser Skylark	13		

(Continue)

Location	Туре	Number	Latitude	Altitude
Gang Cha	Tibetan antelope	6	N36.59' E99.35	3200 (M)
	Kentish Plover	2		
	Great Cormorant	4		
	Common Tern	2		
	Brown Accentor	1		
	Eurasian Hoopoe	5		
Tian Jun	Yellow-billed Chough	2	N37.12' E99.14	3326(M)
	White-rumped Snowfinch	30		
	Blue-fronted Redstart	8		

(Continue)

Location	Туре	Number	Latitude	Altitude
Lake Ke LuKe	Red-crested Pochard	6	N36.59' E99.35'	3200
	Great Crested Grebe	3		
	Little Grebe	2		
	Mongolian Ground-Jay	2		
	Common Coot	1		
	Hill Pigeon	1		
He Ma River	Tree Sparrow	9	N31.52.09' E95.5 6.16'	3250
Xiang Pi mountain	Rufous-tailed Rock-Thrush	1	N36.45.24' E99.3 8.01'	3500
Total: 26		163		

Bioinformatic analysis system

☐ Genomics and evolutionary analysis:

Providing information about genome structure from different subtypes of AI virus, sequences and function of all eight genomic segments, open reading frame of genome and also homology analysis.

□ Proteomics and trans-species spreads of virus:

Studying how the difference in protein sequence affects the infection of various hosts and analyzing interactions between protein-protein, protein-nucleotide and small molecules to understand infecting mechanism and advise drug designs based on protein structures.

Bioinformatic analysis system

- ☐ Bioinformatic analysis software used for our researchers
 - **■** ① GCG:

A comprehensive collection of sequence analysis tools which contains over 140 programs and can be used to perform a gene / genes and protein analysis

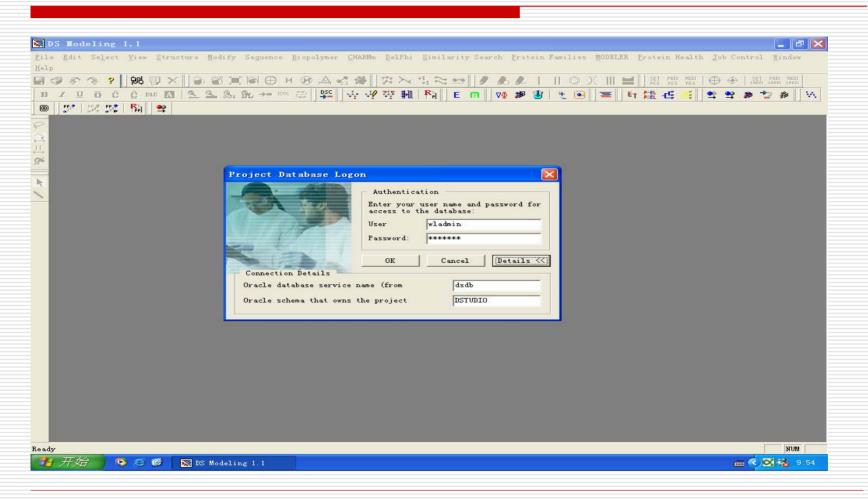
② DS Modeling:

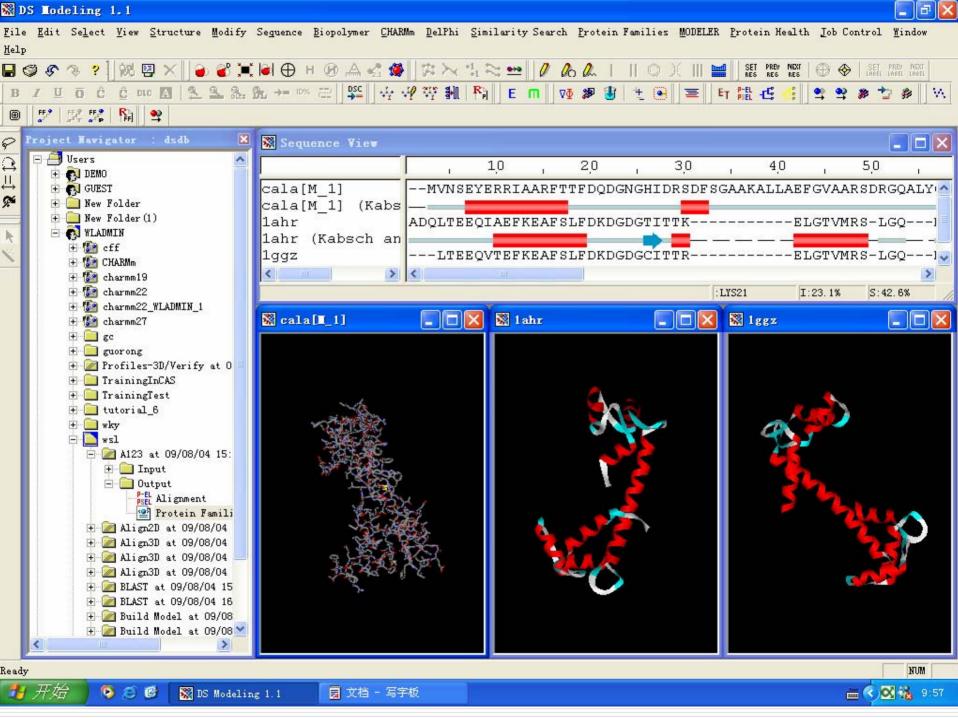
A collection of tools that provide functionality for protein characterization, X-ray analysis, proteomic functional annotation, and homology modeling

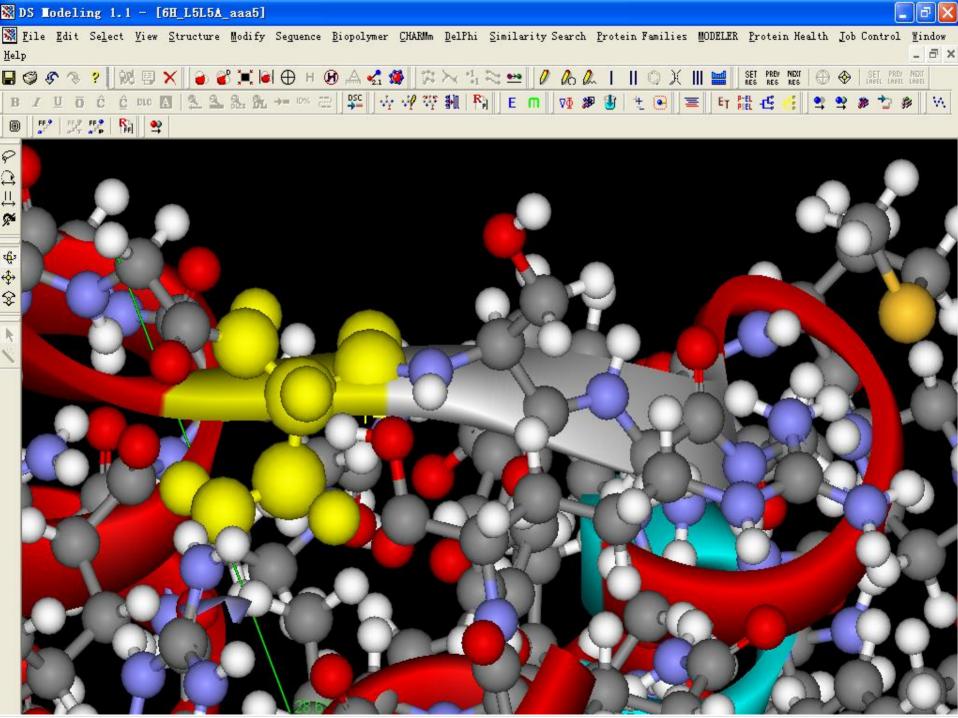
Bioinformatic analysis system

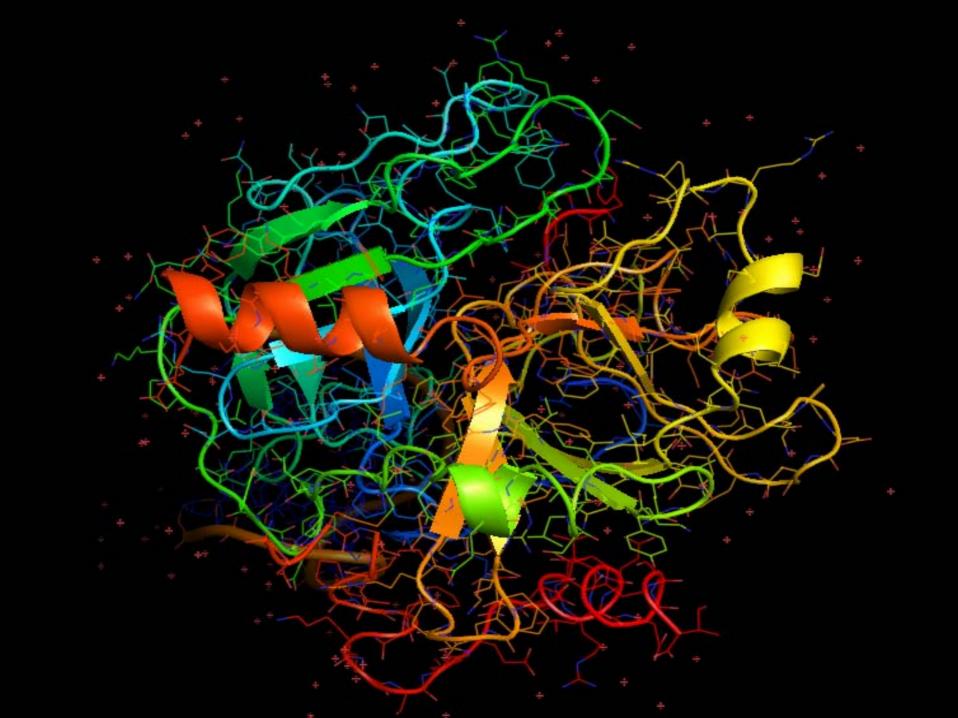
- Bioinformatic platform integrated in publication system for external usages
 - 1. Blast
 - 2. Clustalw
 - 3. Translation
 - 4. Motif searching

DS Modeling 1.1

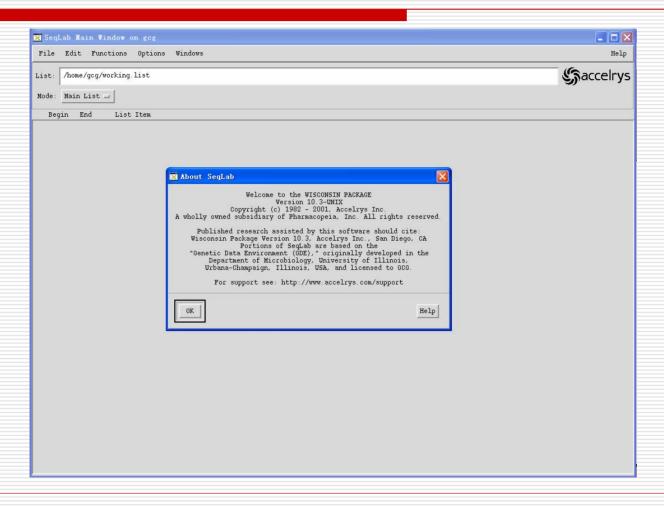








GCG package



Bioinformatic tools integrated in sequence database

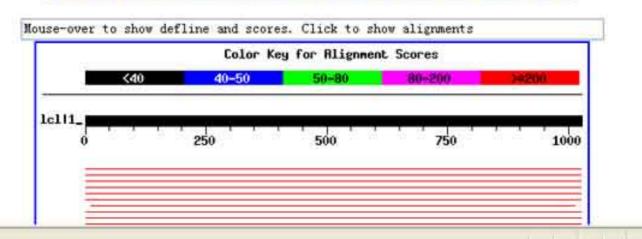


Bioinformatic tools integrated in sequence database

AB013806		
NALEN	710	
NATYPE	RNA	
CIRCULAR	linear	
division	VRL	
date	26-MAR-2003	
definition	Influenza A virus (A/Tokyo/1511/98(H3N2)) gene for hemagglutinin, partial cds.	
accession	AB013806	
versions	["AB013806.1", "GI:4760441"]	
keywords		
source	Influenza A virus (A/Tokyo/1511/98(H3N2))	
organism	Influenza A virus (A/Tokyo/1511/98(H3N2))	
taxonomy	Viruses; ssRNA negative-strand viruses; Orthomyxoviridae; Influenzavirus A.	
comment		
origin		
sequence	ttgttgaacgcagcaaagcttaccgcaactgttacccttatgatgtgccggattatgcctcccttaggtcactagtt gcctcatccggcaccctggagtttaacaatgaaagcttcaattggactggagtcgctcagaatggaacaagctt tgcttgcaaaaggagatctattaaaagtttctttagtagattgaattggttgcaccaattaaaatacaaatacca gcactgaacgtgactatgccaaacaatgacaaatttgacaaattgtacatttggggggttcaccaccccgagtac ggacagtgaccaaaccagcctatatgctcaagcatcagggagagtcacagtctctaccaaaagaagccaac aaactgtaatcccgaatatcggatctagaccctgggtaaggggtgtctccagcagaataagcatctattggac aatagtaaaaccgggagacatacttctgattaacagcacagggaatctaattgctcctcggggttacttcaaaa tacgaagtgggaaaagctcaataatgaggtcagatgcacccattggcaaatgccattctgaatgcatcactcc aaatggaagcattcccaatgacaaaccatttcaaaatgtaaacaggatcacatatggggcctgtcccagatat gttaagcaaaacactctgaaattggcaacagggatgcggaatgta Motif	



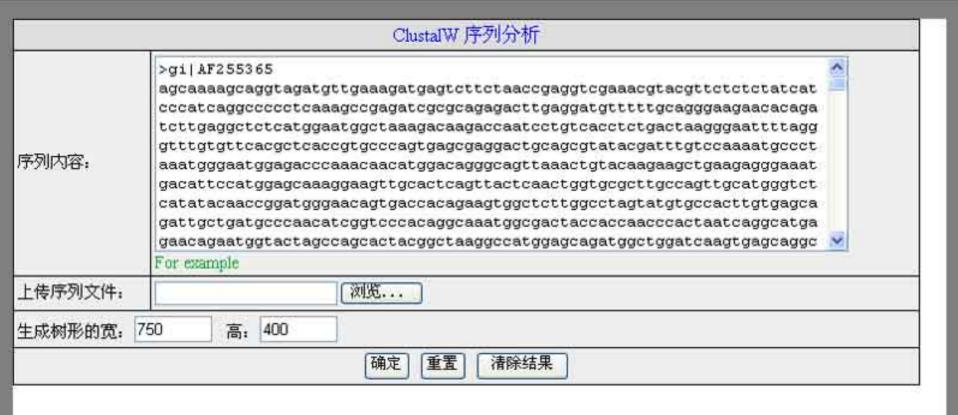
Distribution of 100 Blast Hits on the Query Sequence

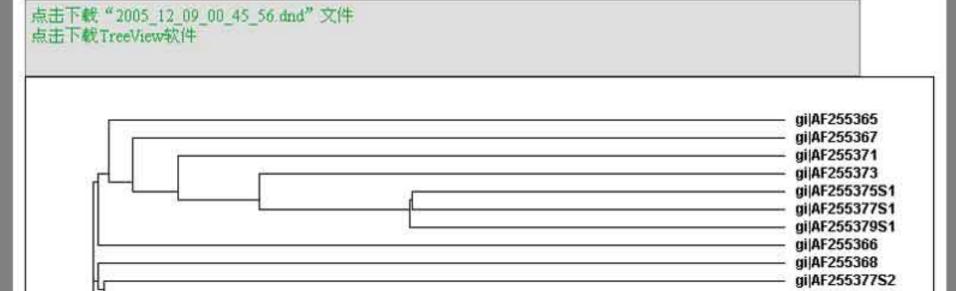


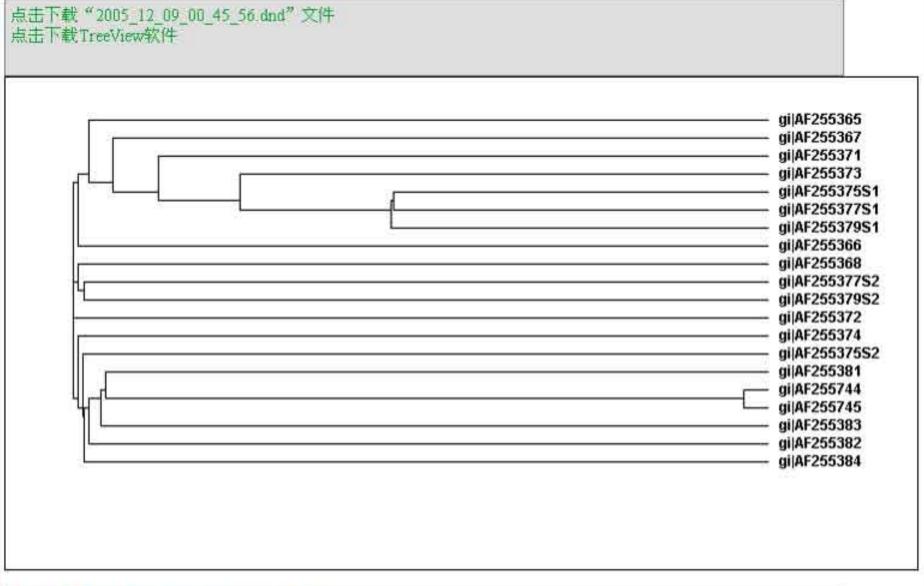
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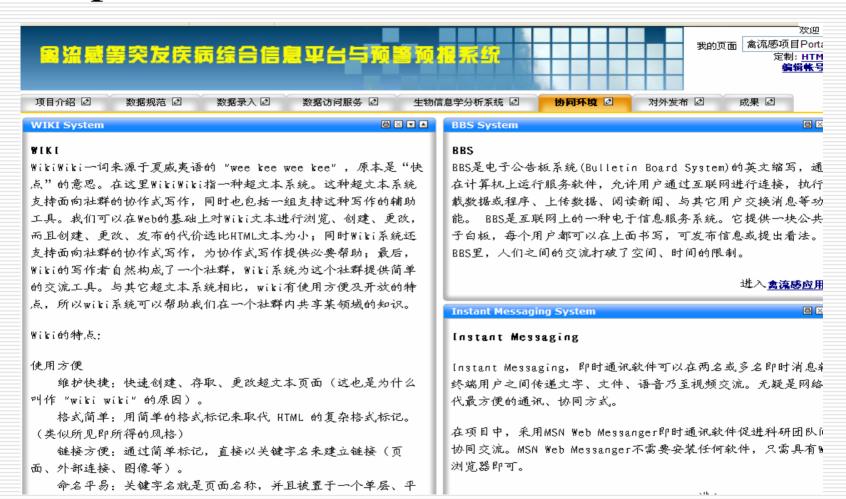




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CLUSTAL W (1.83) multiple sequence alignment

Cooperative Scientific Research Network

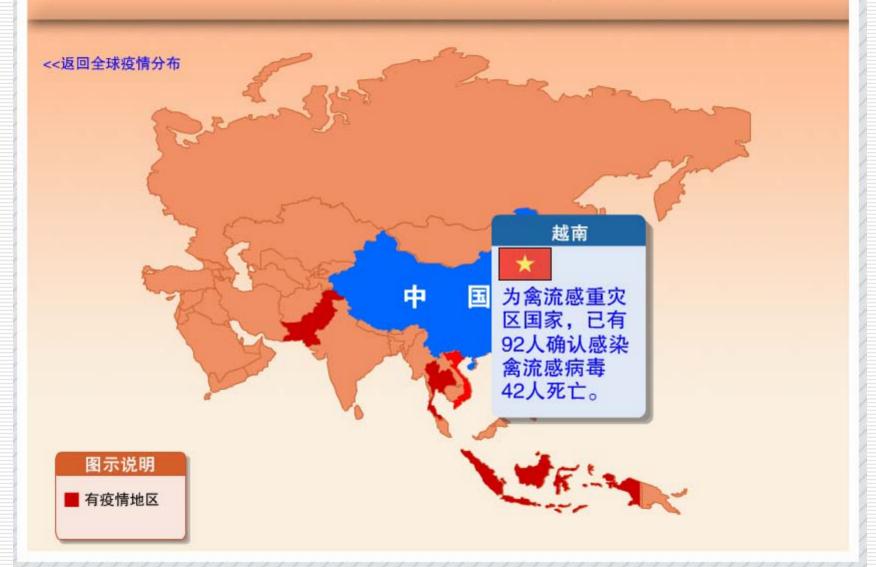


Providing software and tools for cooperative working environment, including: WIKI, BBS, instant messaging, mail lists, FTP services and so on.

Information publication system



全球禽流感疫情分布



全球禽流感疫情分布



What next?

- Conducting serological and pathological investigation of migratory birds and poultry in places along their flyways like Qinghai Lake periodically.
- Getting breakthroughs in virus infecting mechanism, functional protein of virus-host cell protein interactions and trans-species spreading researches.
- Focusing on AI related molecular virology, diagnostic, immunologic researches.
- Ecological and environmental conservational viewpoint of epidemic of this killing disease.

What next?

Data collecting:

Ecological and geographic data Immunological and pathological data

Constructing platforms for:

Data management:

Alarming and predicting system:

Bioinformatic analysis tools:

Setting up network for international cooperation:

Thanks for your attention!