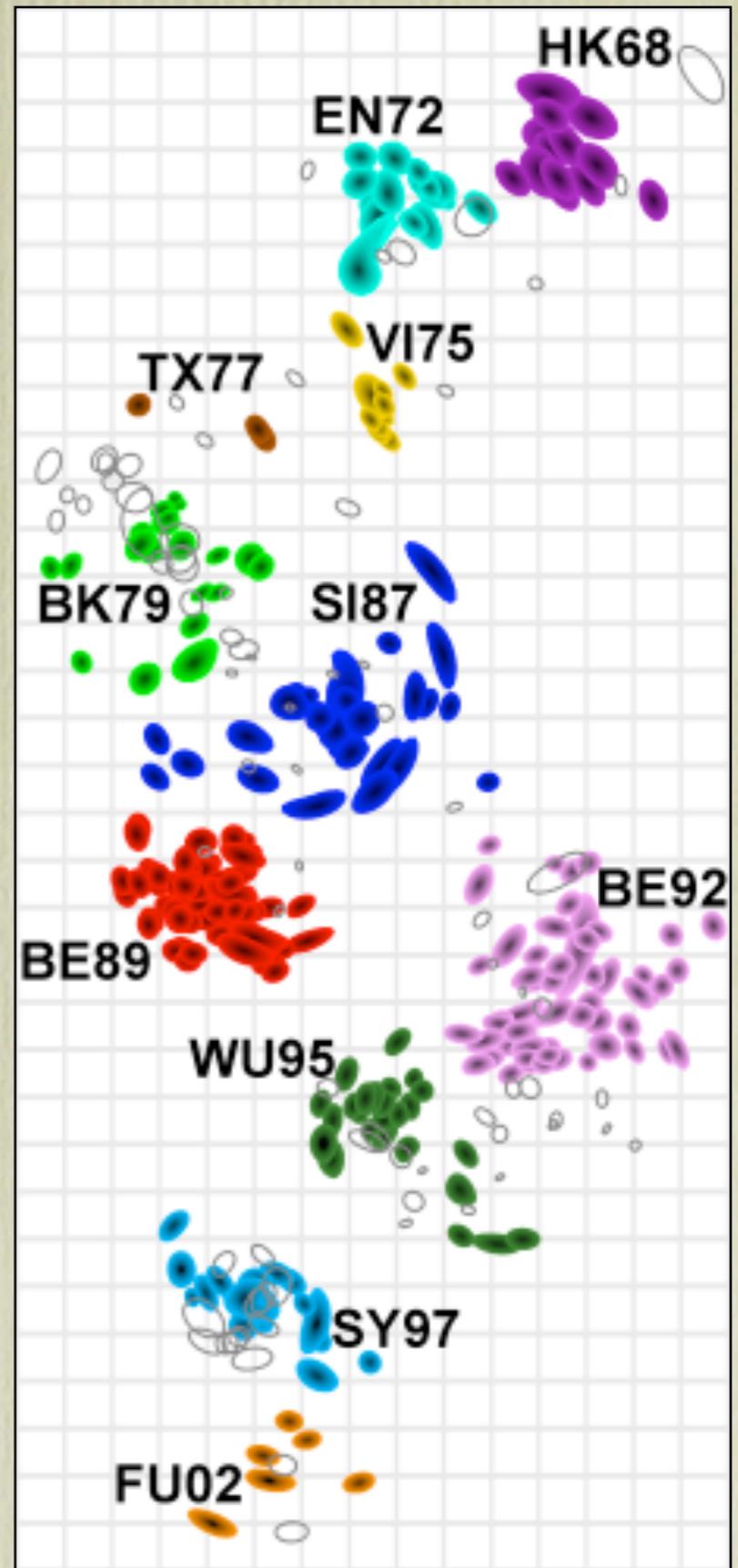


Mapping the antigenic evolution of influenza virus using Antigenic Cartography

Terry Jones

University of Cambridge
&
Charité – Universitätsmedizin, Berlin
tcj25@cam.ac.uk



1 Influenza

Influenza

Epidemic & Pandemic

Pandemic influenza

- 1918 human population: 1.5 billion
- ~500 million (33%) got **very** sick
- ~50 million (3%) **died**

Top killers

<i>Deaths</i>	<i>Event</i>	<i>When</i>
300M+	Smallpox	20 th C
300M+	Plague	14 th -20 th C
80-250M	Malaria	20 th C
40-100M	Tuberculosis	20 th C
50-100M	Spanish flu	1918-1919

Source: Wikipedia

6,000,000 DEATHS FROM INFLUENZA

This Is Estimate For World, For
Past 12 Weeks:

RECALLS BLACK DEATH

"Flu" Five Times Deadlier
Than World War.

LONDON, Dec. 19.—Canadian Press, via Reuter's.)—The Times' medical correspondent says that it seems reasonable to believe that about 6,000,000 persons perished from influenza pneumonia during the past 12 weeks. It has been estimated that the war caused the death of 20,000,000 persons in four and a half years.

Thus, the correspondent points out, influenza has proved itself five times deadlier than war, because, in the same

INFLUENZA DEATH RATE IN ONTARIO

London's Fatality List 326 per 100,000
of Population.

Statistics compiled by Dr. J. W. H. McCallum, chief officer of health for Ontario, indicate that in none of the cities in the province was the death rate from Spanish influenza and complications as great as in the United States centers. Toronto's death rate is given as 327 per 100,000. Kingston was the hardest hit in Ontario, the rate being 643 per 100,000. Winnipeg suffered the most of any Canadian city, according to the figures now available. The death rate in that city was 744 per 100,000.

Camp Sheridan, Ont., where 22,000 soldiers were encamped, had the heaviest death rate of all, it being 2,661 in total of population.

The figures, which cover an approximate period of six weeks, are

Cities.	Deaths from Influenza and Complications.	Death Rate per 100,000 Population	
		Deaths	Pneumonia.
Port William	46	326	
Haut Rte. Marie	41	319	
Ottawa	570	643	
Port Arthur	30	191	
Winnipeg	31	105	
Kitchener	146	644	
London	187	326	
Toronto	1,800	327	
Rt. John, N.B.	126	294	
Montreal	368	744	
Halifax	226	489	
Hamilton	163	379	
United States Figures			
Boston	3,064	321	
Pittsburgh	3,894	721	
Philadelphia	12,887	819	
Washington	1,864	591	
Camp Sheridan, O.	842	2,661	
New York	22,960	600	

1489 EMPLOYEES ABSENT TODAY

B.M.HOLDEN,

DEPOT QUARTERMASTER.

Philadelphia, Pa.

OCT. 8, 1918.

Col. L.A.Nicolson,

Operating Division, Office Quartermaster General.

Washington, D.C.

EPIDEMIC SPANISH INFLUENZA HAMPERING OPERATIONS OF DEPOT

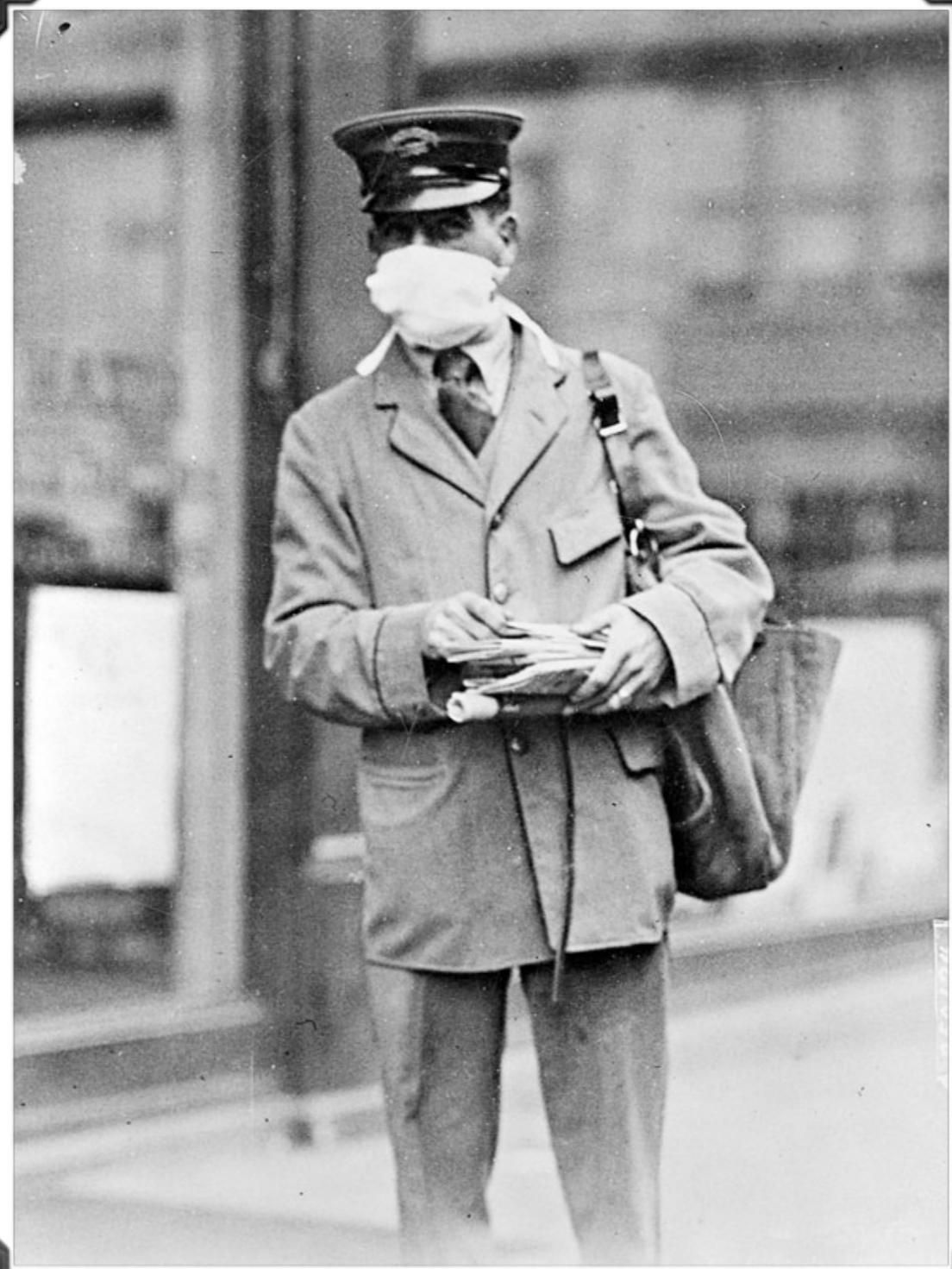
ELEVEN COMMISSIONED OFFICERS AND FOURTEEN HUNDRED EIGHTY NINE

EMPLOYEES ABSENT TODAY . OF THE LATTER ELEVEN HUNDRED

SEVENTY SEVEN WORK IN FACTORIES. SITUATION NOT IMPROVING.

HOLDEN.

SITUATION NOT IMPROVING

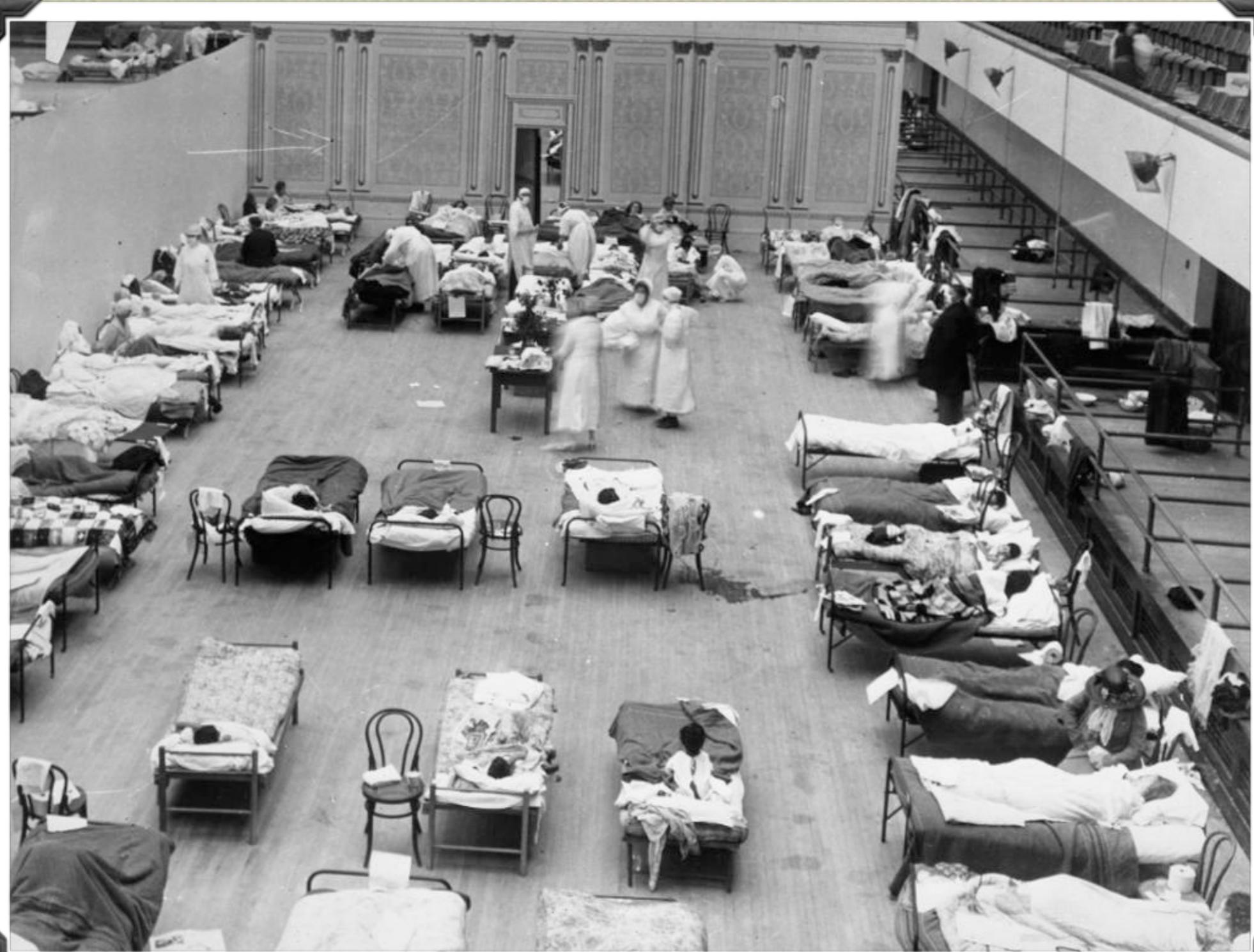




















PATRIOTIC DRIVE AGAINST THE "FLU"

An onion car arrived today,
Labelled red, white and blue,
"Eat onions, plenty, every day,
And keep away the 'Flu'."

Cabbage, too, they vend down
there,
At the Bessemer Transfer track,
Solid heads, three cents the
pound,
Enough to supply the town.

So take a trip out Kittanning St.
And see what you can buy,
With what is left from Liberty
Bonds,
Lay in your winter supply.

Eat More **ONIONS**

**One of the Best Preventatives
for Influenza.**

Car Load of Onions will be on sale
on siding at Bessemer Freight
Station

**TODAY and TOMORROW
Will Be Sold Direct from Car
Bring Your Own Sacks or Baskets if Possible
THE PRICES ARE RIGHT**

J. W. GARDOCKY, Grower

CREAM APPLIED IN NOSTRILS MAY PREVENT SPANISH INFLUENZA

Says Cream Applied in Nostrils
Opens Air Passages
Right Up.

Instant relief—no waiting. Your clogged nostrils open right up; the air passages of your head clear and you can breathe freely. No more hawking, sniffing, blowing, headache, dryness. No struggling for

breath at night; your cold or catarrh disappears.

Get a small bottle of Ely's Cream Balm from your druggist now. Apply a little of this fragrant, anti-septic, healing cream in your nostrils. It penetrates through every air passage of the head, soothes the inflamed or swollen mucous membrane and relief comes instantly.

It's just fine. Don't stay stuffed-up with a cold or nasty catarrh.—
Adv.

SPANISH INFLUENZA

BLOW IT AND INHALE

Dr. Jones' Liniment

COMMONLY KNOWN AS

BEAVER OIL



WHAT'S NEW?

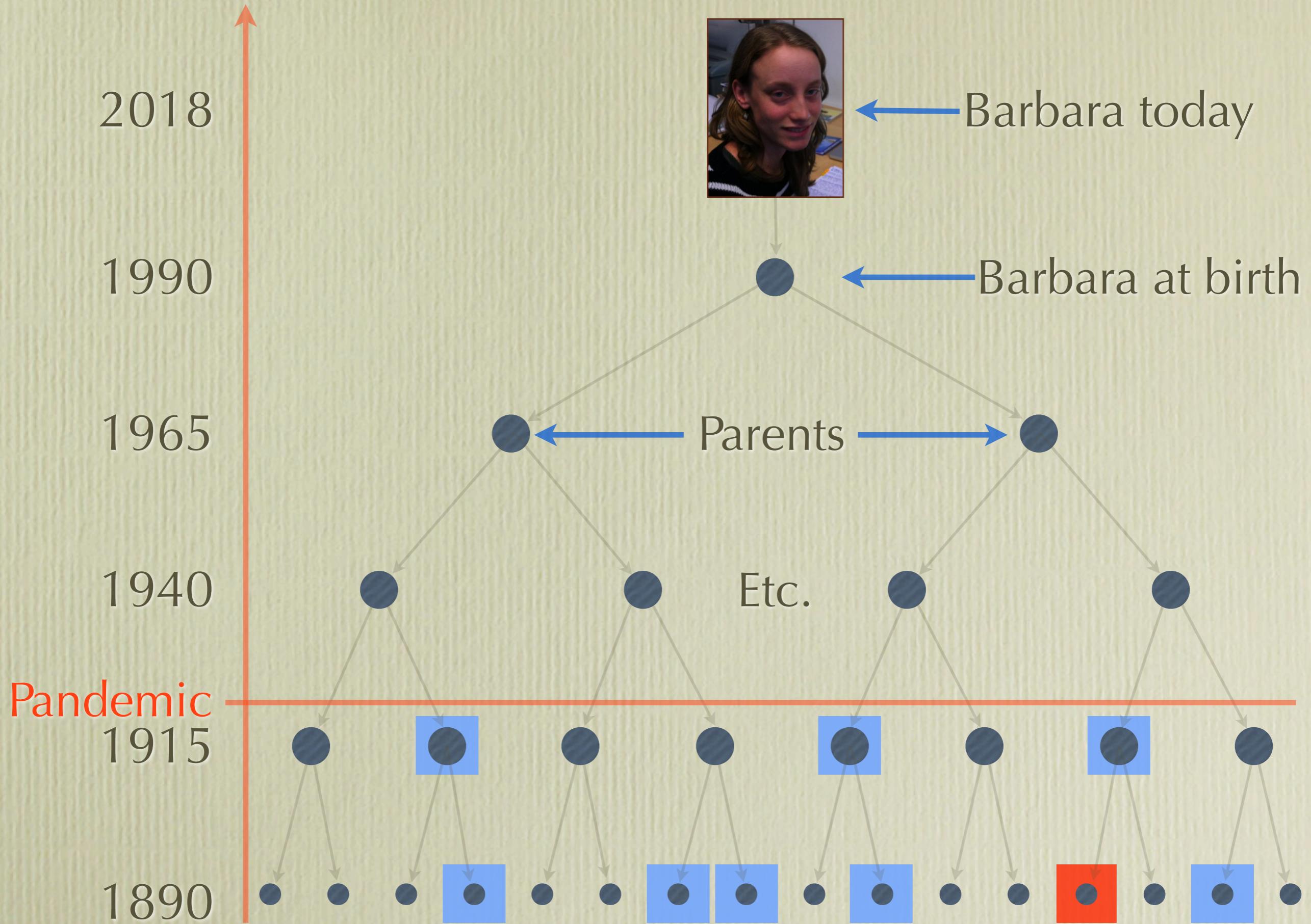
and get relief. Good for cold in chest and extremities. It reduces swelling, inflammation, and is a powerful disinfectant and preservative. Dr. Jones' Liniment is good for the soldier boys in training.

In the home, shop, store—in fact everywhere. Always good to have on hand as a first aid panacea.

All Druggists

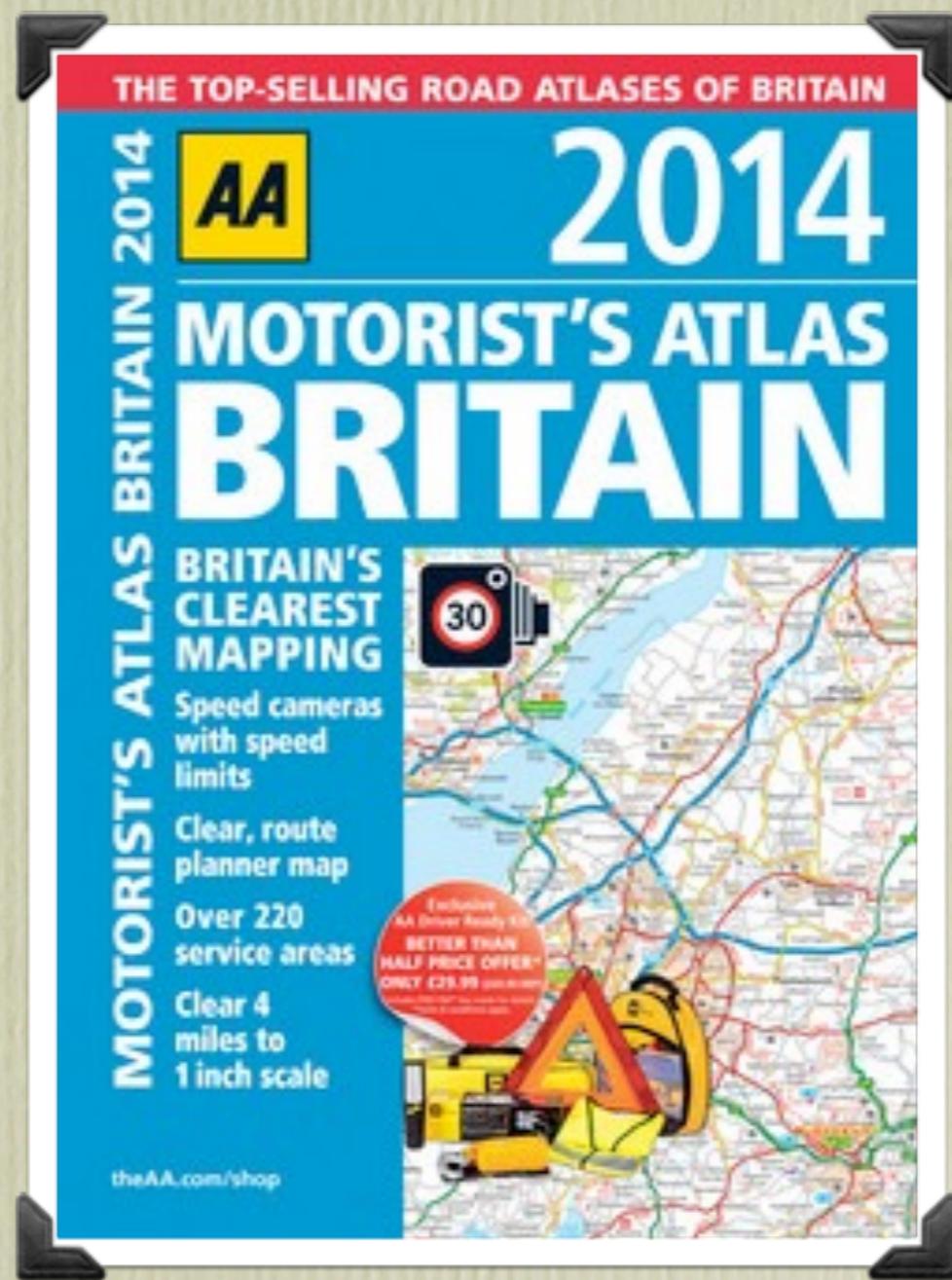
- - - - 30 and 55 Cents





2 Cartography

Retro: street atlas



Distance table

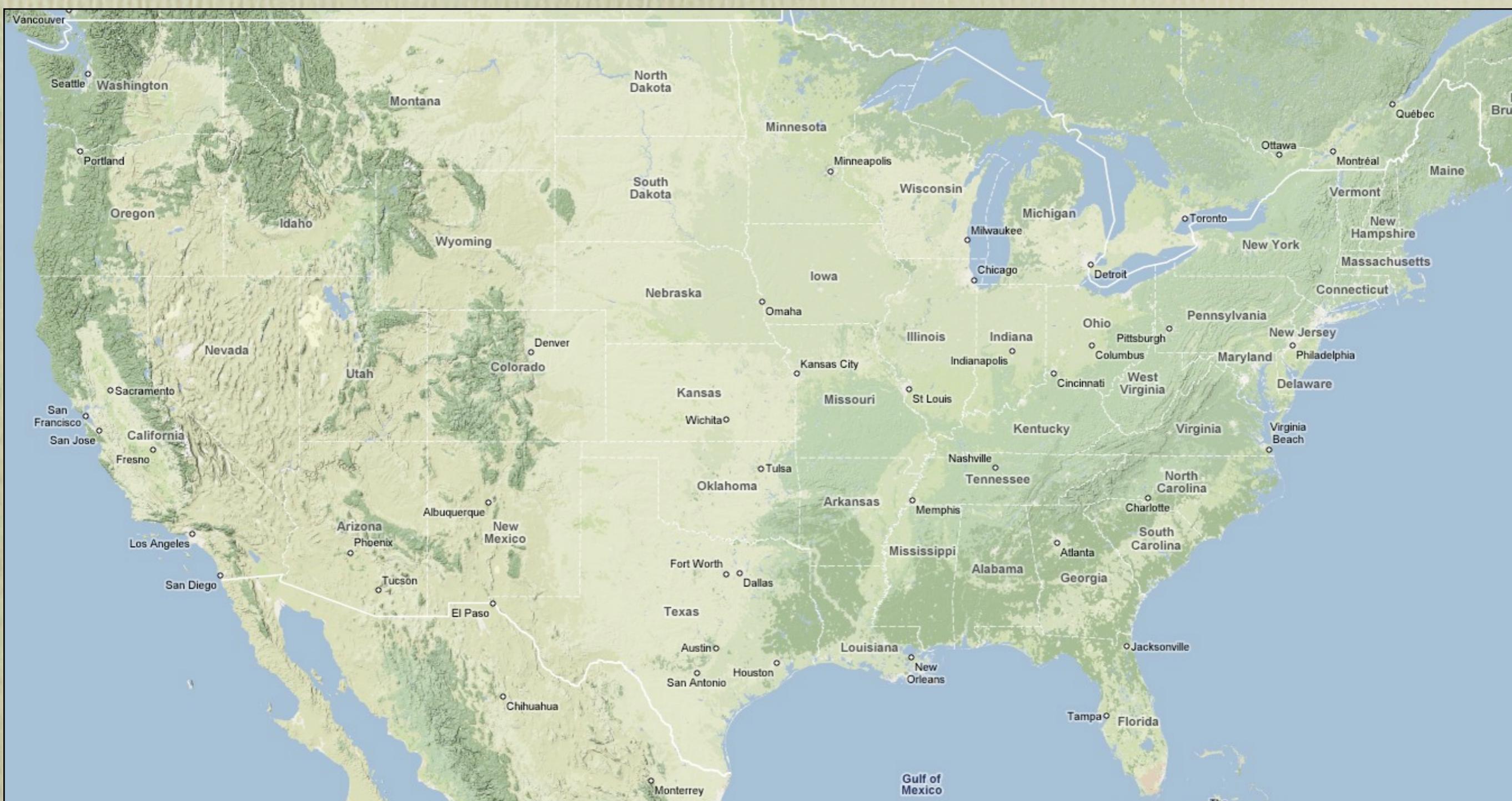
**LANCASHIRE
with some
Confining
Towns**

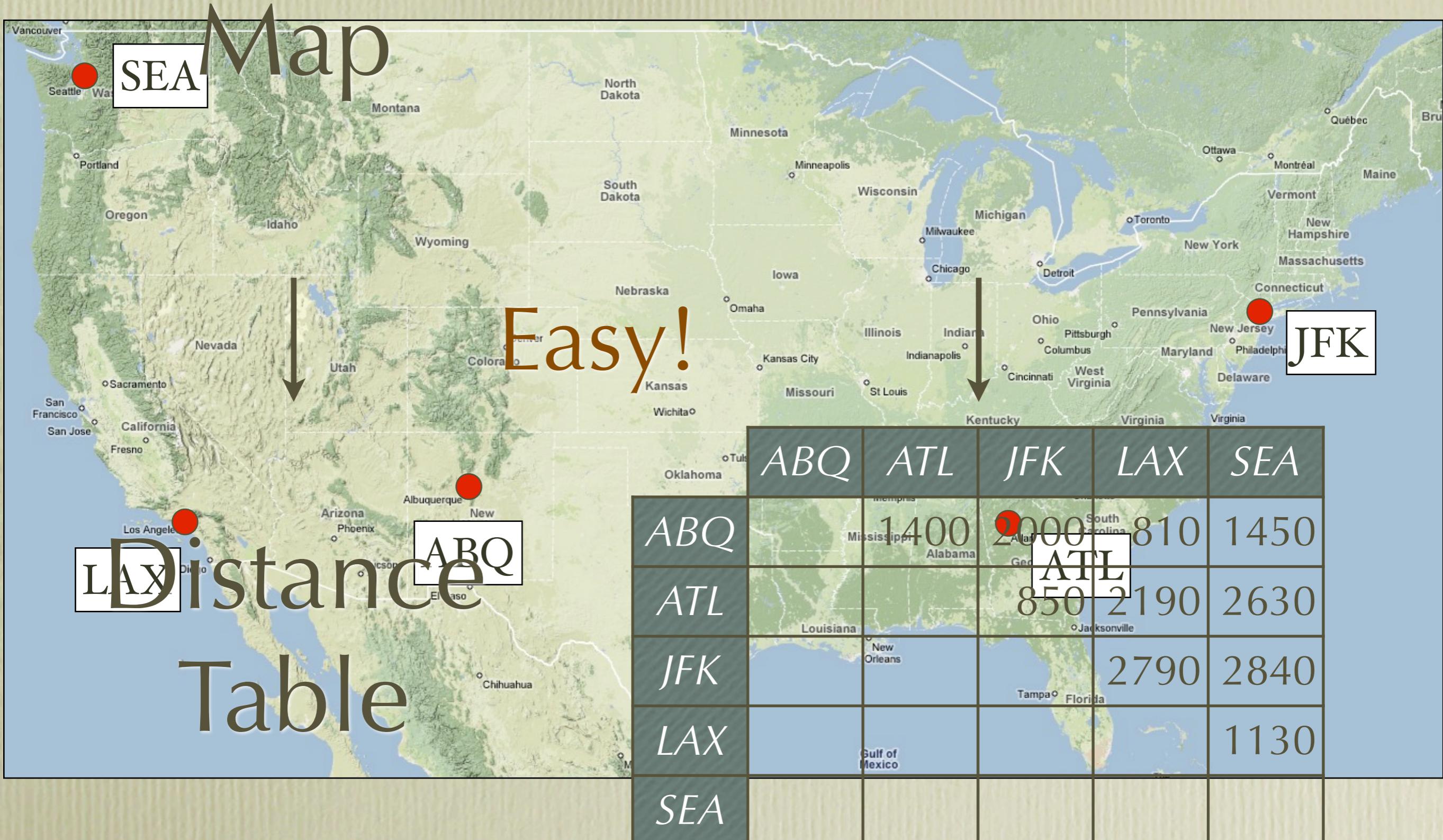
	Lancaster	Preston	Kirkham	Ormeskirke	Leverpool	Warrington	Wygan	Bolton	Bury	Rochdale	Manchester	Blackborne	Gisborne Yor	Colne	Garstrange	Clethero Caste	Wierdale	Hornby Caste	Thurland Caste	Bolton paſſage	Carlone paſſage	Cunywide paſſage	Vinterſtone	Glaystone Caste	Dalton Caste	Kirkby Langd		
Hendal Wym N	25	30	30	40	40	50	40	40	40	40	40	32	24	30	27	27	19	13	12	12	10	14	10	17	17	10	21	204
Kirkby Land NE	10	22	23	33	42	40	33	31	21	31	37	23	15	21	16	18	11	5	3	9	11	17	17	10	21	204		
Dalton Caste N	15	20	26	10	45	47	39	40	43	45	40	35	33	38	22	33	22	20	21	14	10	4	3	3	202			
Glaystone Caste N	14	27	24	34	43	46	38	38	42	43	47	32	31	37	20	21	10	19	19	12	9	4	5	199				
Vluerston NW	13	20	26	36	45	48	40	40	42	44	48	33	30	37	27	31	20	18	18	12	7	2	203					
Cunywide paſſage	13	27	25	35	42	46	38	10	20	42	40	32	20	35	20	30	18	16	17	10	6	198						
Carlone paſſage	0	25	23	34	42	44	36	38	17	38	44	2	25	31	17	25	14	11	11	6	194							
Bolto paſſage N.	3	10	16	28	37	38	29	30	30	31	36	22	18	24	11	18	8	6	8	LANCASHIRE								
Thurland Caste	8	14	20	31	40	38	30	28	29	29	35	20	13	19	14	15	8	3	19	sends								
Hornby Caste NE	6	18	19	20	37	36	28	27	28	28	33	19	13	19	12	14	7	186	XIV Members									
Wyersdale SE	5	12	12	23	30	30	21	22	27	24	20	14	12	17	5	12	180		to									
Clethero Caste	17	12	16	22	31	25	18	14	13	13	19	7	5	6	13	16		Parliament	has									
Garstrange S.	8	8	7	17	25	26	18	19	21	23	27	13	16	20	181													
Colne S.E.	23	27	22	27	34	27	21	16	14	12	19	11	6	165														
Gisborne Yors	17	16	20	28	35	39	23	19	18	17	23	12	140															
Blackeborne	19	7	12	16	23	18	11	8	0	10	15	105																
Manchester S	34	20	24	21	24	12	13	8	6	9	140																	
Rochdale S.E.	29	17	22	22	27	17	14	8	4	154																		
Bury S.E.	28	14	10	18	13	14	10	4	16																			
Bolton S.E.	20	12	16	14	20	11	7	170																				
Wygan S.E.	26	11	14	8	13	8	150																					
Warrington S	15	10	22	19	19	19	100																					
Leverpoole S	34	20	20	9	160																							
Ormeskirke S	26	12	11	170																								
Kirkham S	15	6	167																									
Preston S.E.	16	109																										

Lancashire *Lancaster* *Newton* *Wigan* *Clethero* *Leverpoole*

Kirkby Langd

LANCASHIRE
with some Confining Towns
sends
XIV Members
to Parliament
has
XXII Market Towns
and
36 Parishes
is divided into
Hundreds
containing
about 1150000 Acres
and about
40202 Houses
and above
240000 Inhabitants
In compass
170 Miles





Can we go the other way?

Distance table → Map

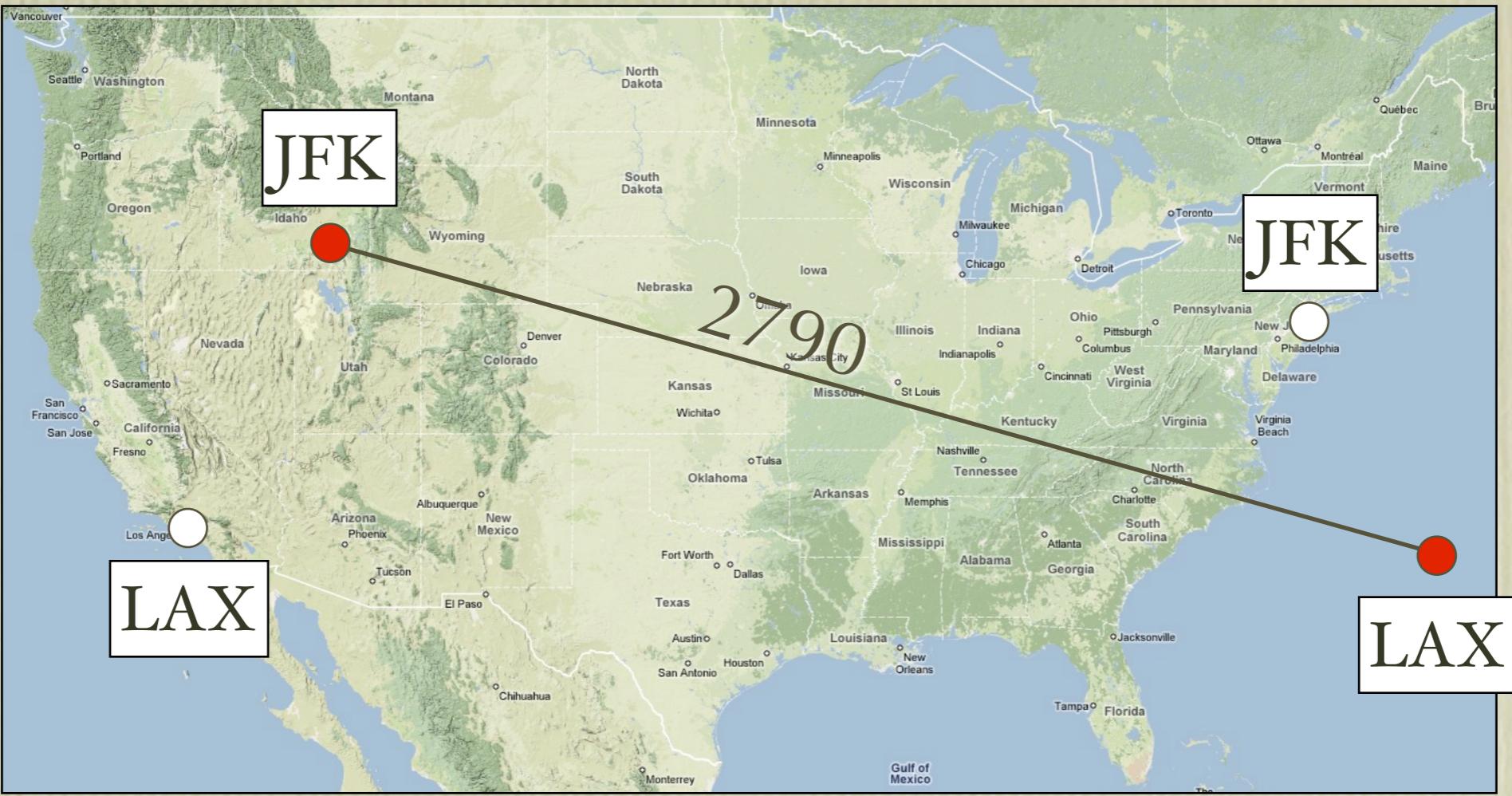
Distance table

	<i>ABQ</i>	<i>ATL</i>	<i>JFK</i>	<i>LAX</i>	<i>SEA</i>
<i>ABQ</i>		1400	2000	810	1450
<i>ATL</i>				850	2190
<i>JFK</i>					2790
<i>LAX</i>					1130
<i>SEA</i>					

Hmm...

Map

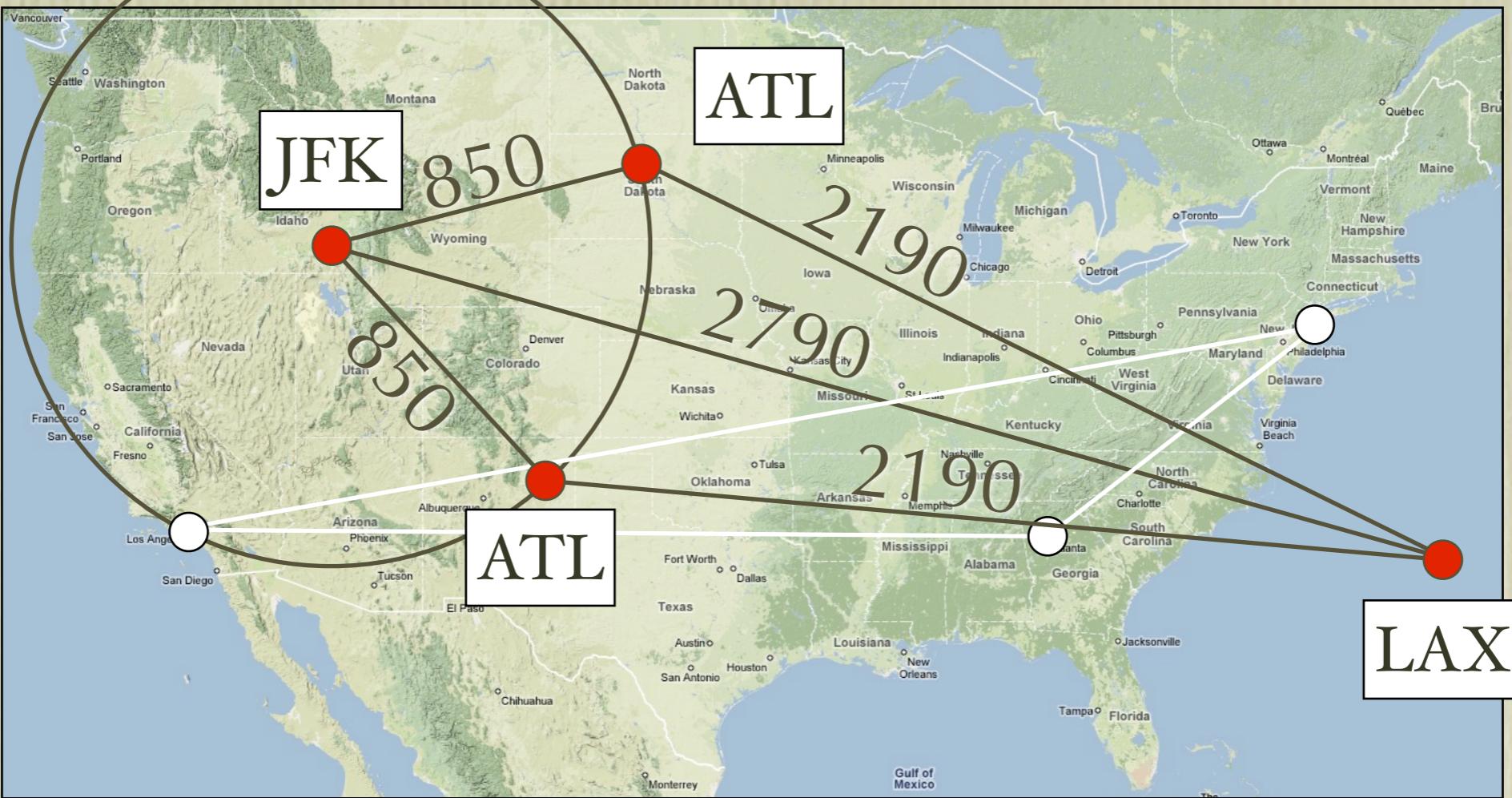




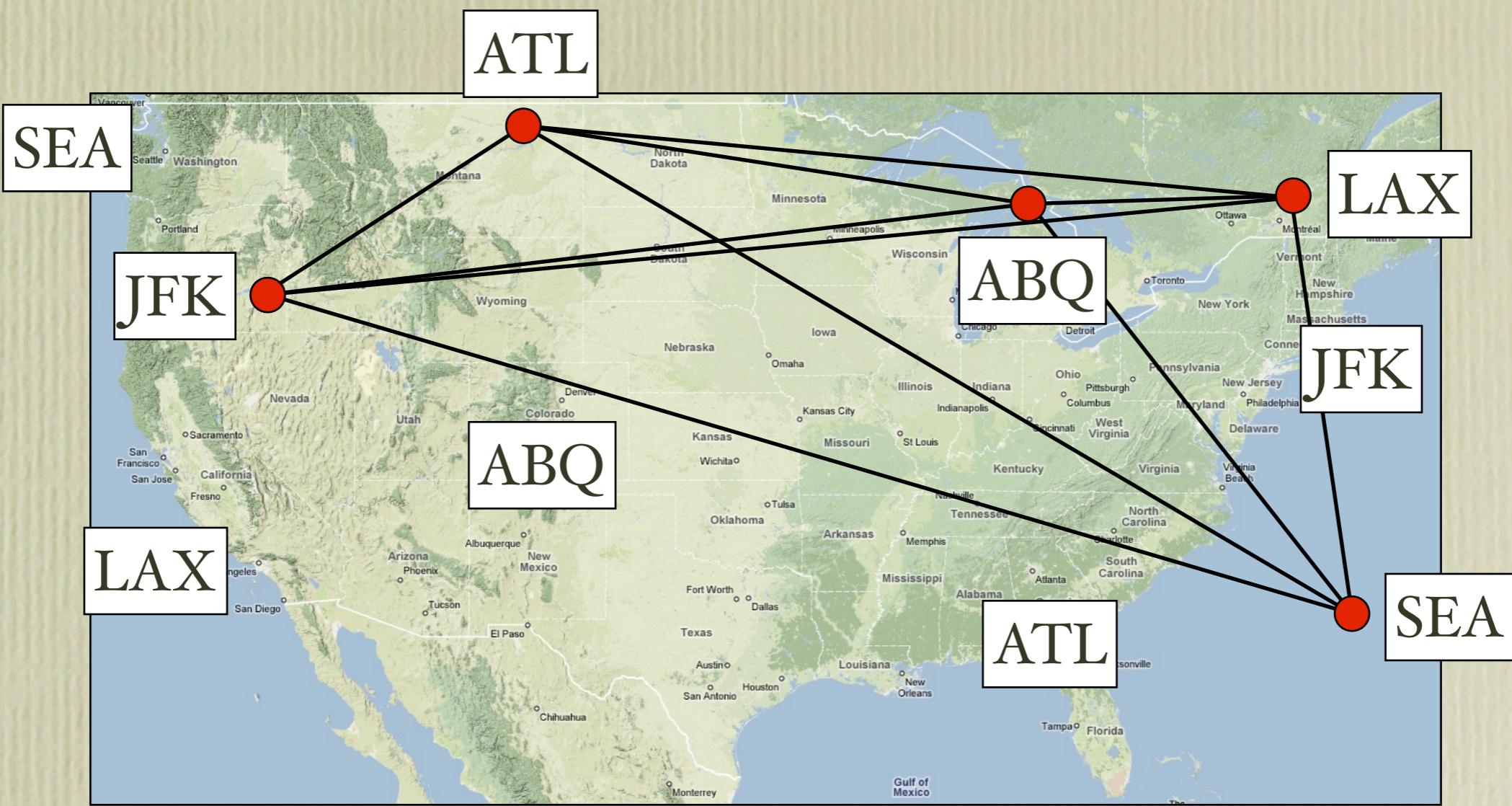
	ATL	JFK	LAX	SEA
ABQ				
ATL				
JFK			2790	
LAX				



	<i>ATL</i>	<i>JFK</i>	<i>LAX</i>	<i>SEA</i>
<i>ABQ</i>				
<i>ATL</i>		850		
<i>JFK</i>			2790	
<i>LAX</i>				



	<i>ATL</i>	<i>JFK</i>	<i>LAX</i>	<i>SEA</i>
<i>ABQ</i>				
<i>ATL</i>		850	2190	
<i>JFK</i>			2790	
<i>LAX</i>				



	<i>ATL</i>	<i>JFK</i>	<i>LAX</i>	<i>SEA</i>
<i>ABQ</i>	1400	2000	810	1450
<i>ATL</i>		850	2190	2630
<i>JFK</i>			2790	2840
<i>LAX</i>				1130

3

Antigenic
cartography

Epidemic influenza

- 10-15% of people infected each year
- 250-500K die each year
- Vaccine composition reviewed twice a year
- Antigenically variable ssRNA virus

Influenza vaccine

- Human epidemic vaccine is based on 3 viral strains
- ~400M vaccine doses annually
- Strain selection committee
- Vaccine composition reviewed twice a year
- How do they decide what to put in the vaccine?

H3N2 data

- HI assay
 - 1500 measurements
 - 20-50 tables
 - 4 international labs
 - ~114 national labs

What could go wrong?

	<i>ATL</i>	<i>JFK</i>	<i>LAX</i>	<i>SEA</i>
<i>ABQ</i>	1400	2000	810	1450
<i>ATL</i>		850	2190	2630
<i>JFK</i>			2790	22840
<i>LAX</i>	2300			1130

What could go wrong?

Rounded

	<i>ATL</i>	<i>JFK</i>	<i>LAX</i>	<i>SEA</i>
<i>ABQ</i>	1400	2000		
<i>ATL</i>		850	2190	2630
<i>JFK</i>			2790	22840
<i>LAX</i>	2300			1130

Missing

Inconsistent

Wrong

The diagram illustrates several types of data inconsistency in a flight schedule matrix:

- Rounded:** The value 2000 in the *ABQ-JFK* cell is labeled "Rounded", indicating it has been simplified from its original value.
- Missing:** The empty cells in the *LAX* row are labeled "Missing", suggesting some data is missing or needs to be filled.
- Wrong:** The value 22840 in the *JFK-SEA* cell is labeled "Wrong", likely due to a calculation error or incorrect input.
- Inconsistent:** The value 2300 in the *LAX-ABQ* cell is labeled "Inconsistent", possibly referring to a discrepancy with other data or a specific rule being violated.

Oops...



Oops...



Oops...

Google Maps

Web Images Video News Maps more »

19020 | 1579 US-1 (S), North Brunswick.

Search the map Find businesses Get directions

Maps

Get reverse directions

From: PA 19020

Drive: 37.4 mi (about 54 mins)

1.	Head southeast on Galloway Rd toward Hulmeville Rd	0.1 mi
2.	Turn left at Hulmeville Rd	2.6 mi
3.	Turn left at Neshaminy St	0.1 mi
4.	Slight right at Bellevue Ave	1.8 mi
5.	Turn right to merge onto US-1 N	0.6 mi
6.	Make a U-turn	0.2 mi
7.	Make a U-turn	335 ft
8.	Make a U-turn	0.2 mi
9.	Make a U-turn	1.1 mi
10.	Make a U-turn	0.2 mi
11.	Make a U-turn	0.1 mi
12.	Make a U-turn	285 ft
13.	Make a U-turn	0.1 mi
14.	Make a U-turn	125 ft
15.	Make a U-turn	0.2 mi
16.	Make a U-turn	282 ft
17.	Make a U-turn	0.1 mi
18.	Make a U-turn	253 ft
19.	Make a U-turn	115 ft
20.	Make a U-turn	0.6 mi

The map displays a route starting from PA 19020 in Bethlehem, moving southeast along Galloway Rd, then turning left onto Hulmeville Rd, left onto Neshaminy St, right onto Bellevue Ave, and finally merging onto US-1 N. The route then requires 19 more U-turns to reach the final destination, 1579 US-1 (S), North Brunswick. The map also shows Route 31, Route 22, and Spruce Run State Park.

Oops...

Google Maps

Web Images Video News Maps more »

Stanford, California, United States ➔ KTH-hallen, Stockholm, Sweden Get Directions

Search the map Find businesses Get directions

Print Email Link to this page

Maps

29. Take exit 24 A-B-C on the left toward I-93 N/Concord NH/S Station/I-93 S/Quincy 0.4 mi

30. Merge onto Atlantic Ave 0.8 mi

31. Turn right at Central St 0.1 mi

32. Turn right at Long Wharf 0.1 mi

33. Swim across the Atlantic Ocean 3,462 mi

34. Slight right at E05 0.5 mi

35. At the roundabout, take the 2nd exit onto E05/Pont Vauban 0.1 mi

36. Turn right at E05 5.7 mi

37. Take the exit onto A29/E44 toward Amiens Toll road 27.8 mi

38. Take the exit toward Dieppe/Amiens/Calais/A151/Rouen 1.1 mi

Traffic Map Satellite Hybrid

Greenland

Iceland

Suomi Finland

Norge

United Kingdom

Polska

Deutschland

France

Espania

Algeria

Canada

North Atlantic Ocean

United States

Mexico

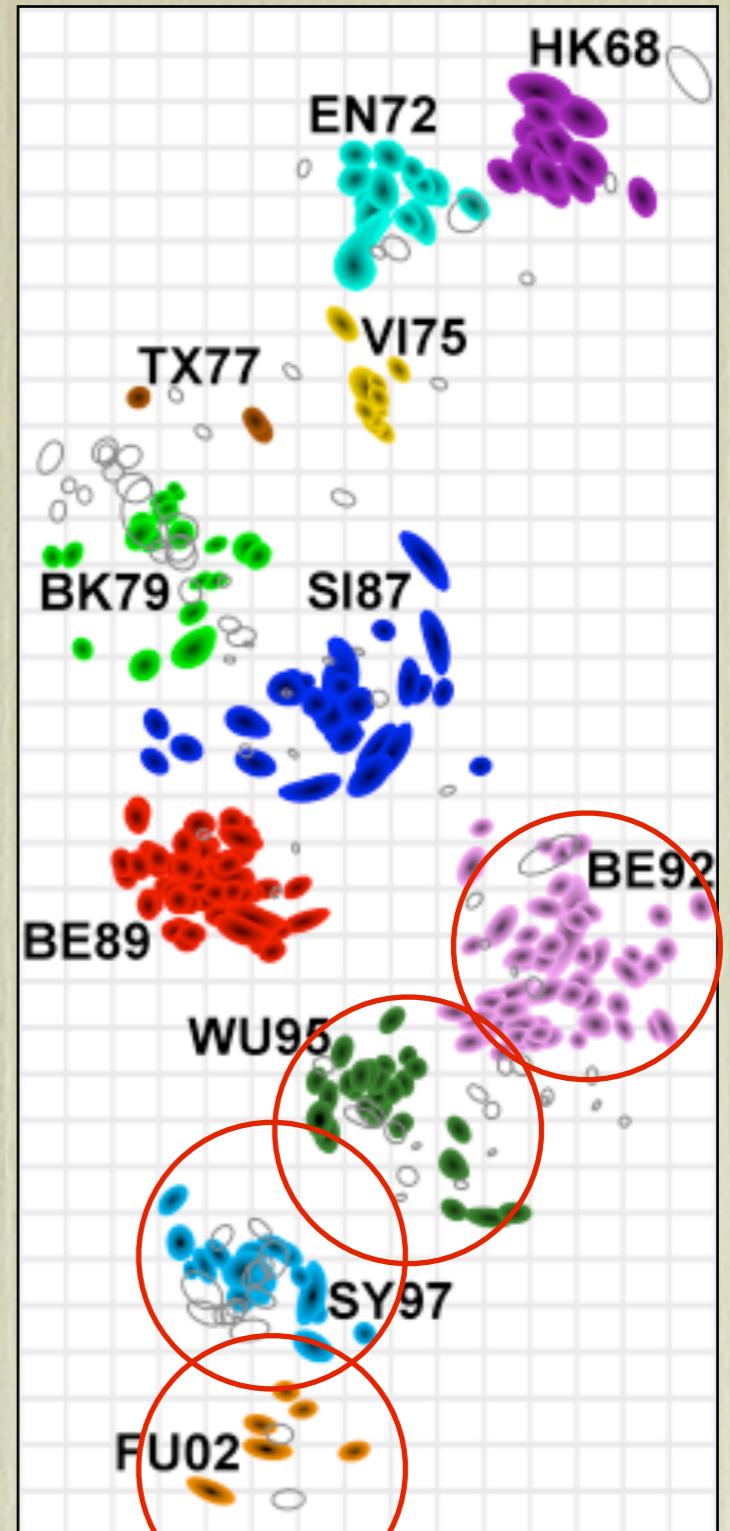
1000 mi
2000 km

©2007 Google - Map data ©2007 European Institute of Use

Antigenic maps

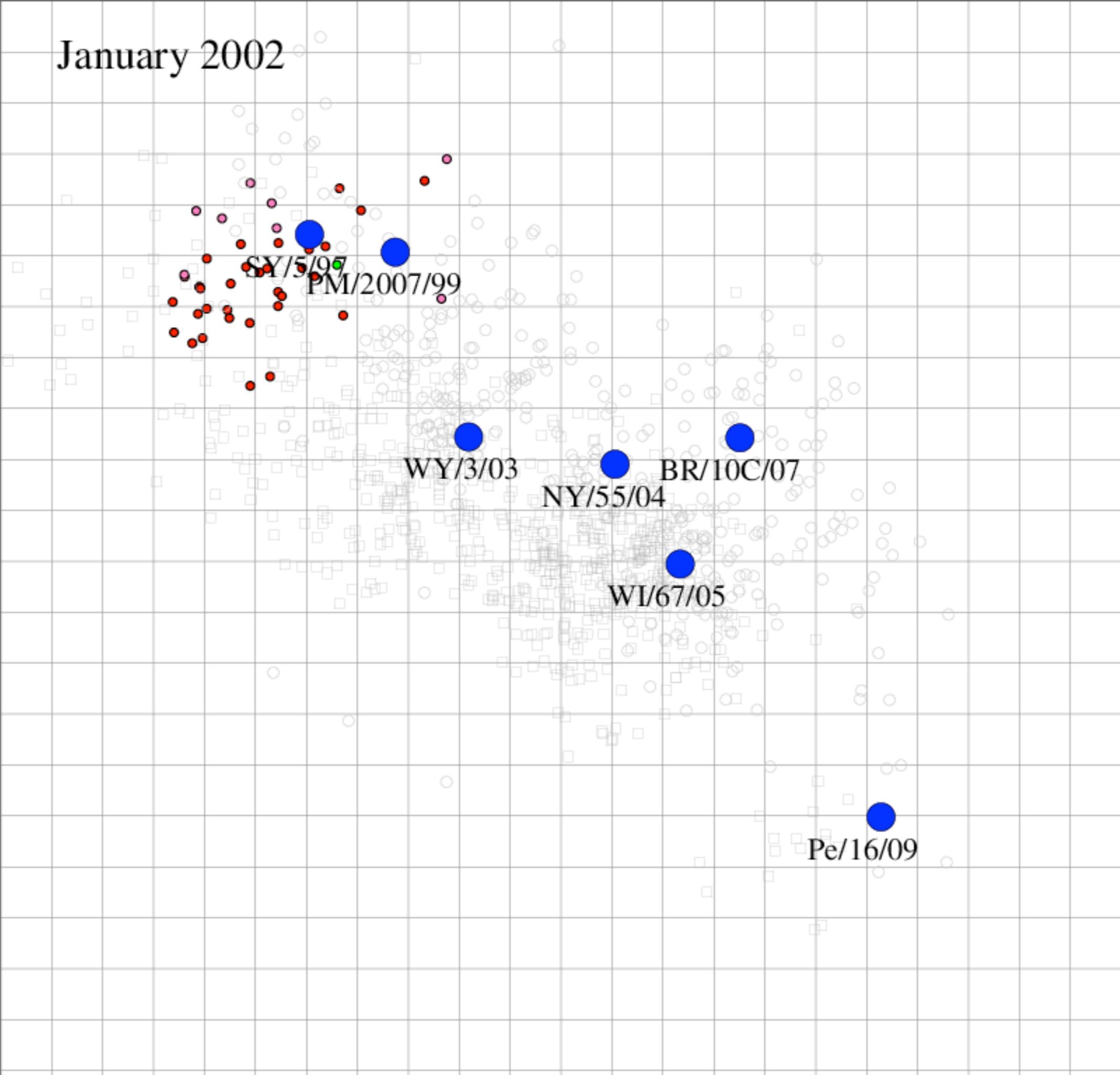
35 years of influenza evolution

- Two dimensional
- Clustered, with discreet transitions
- Roughly equal cluster gaps
- Roughly equal timing between clusters
- Mostly linear?
- Predictable?

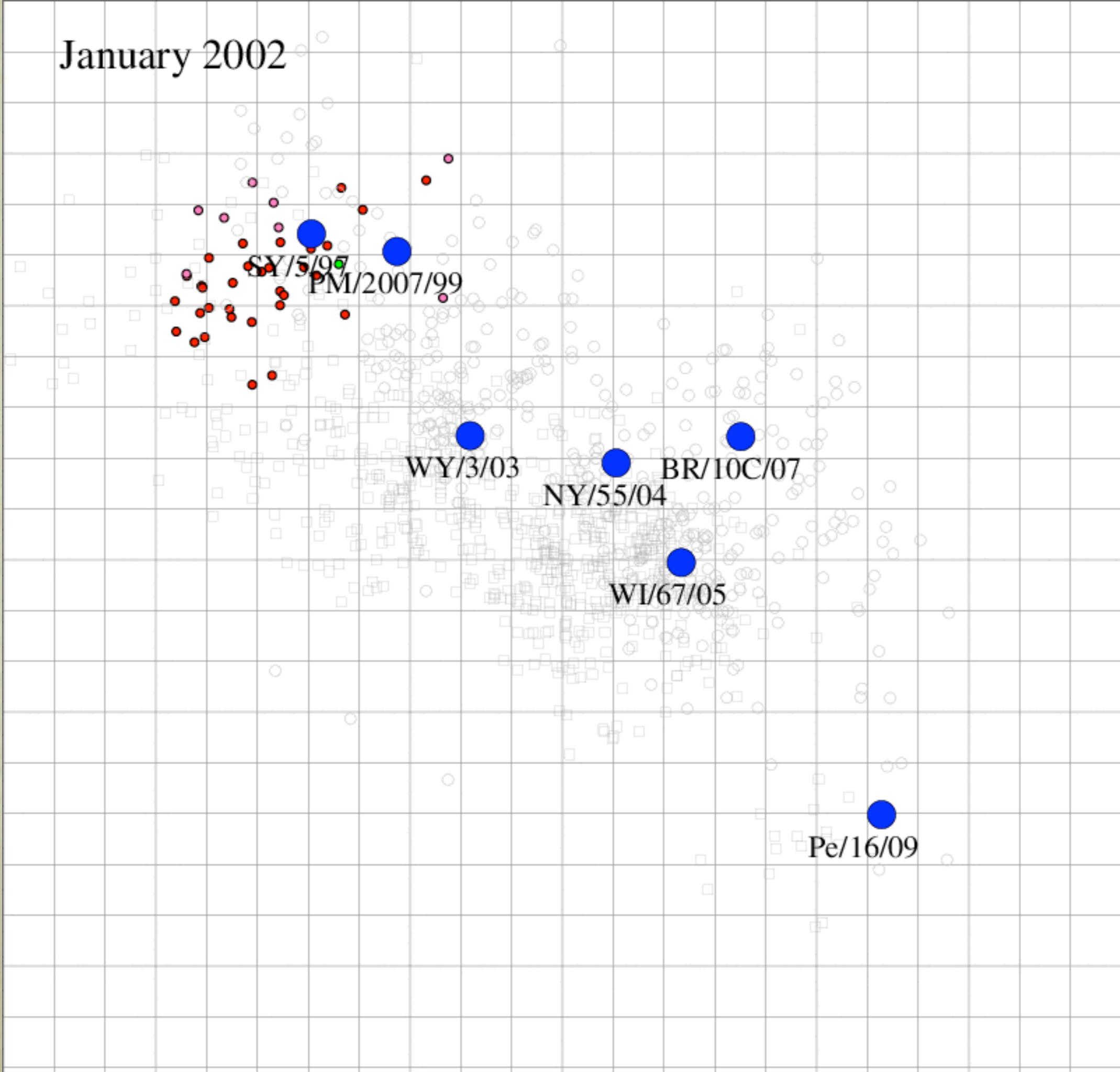


?

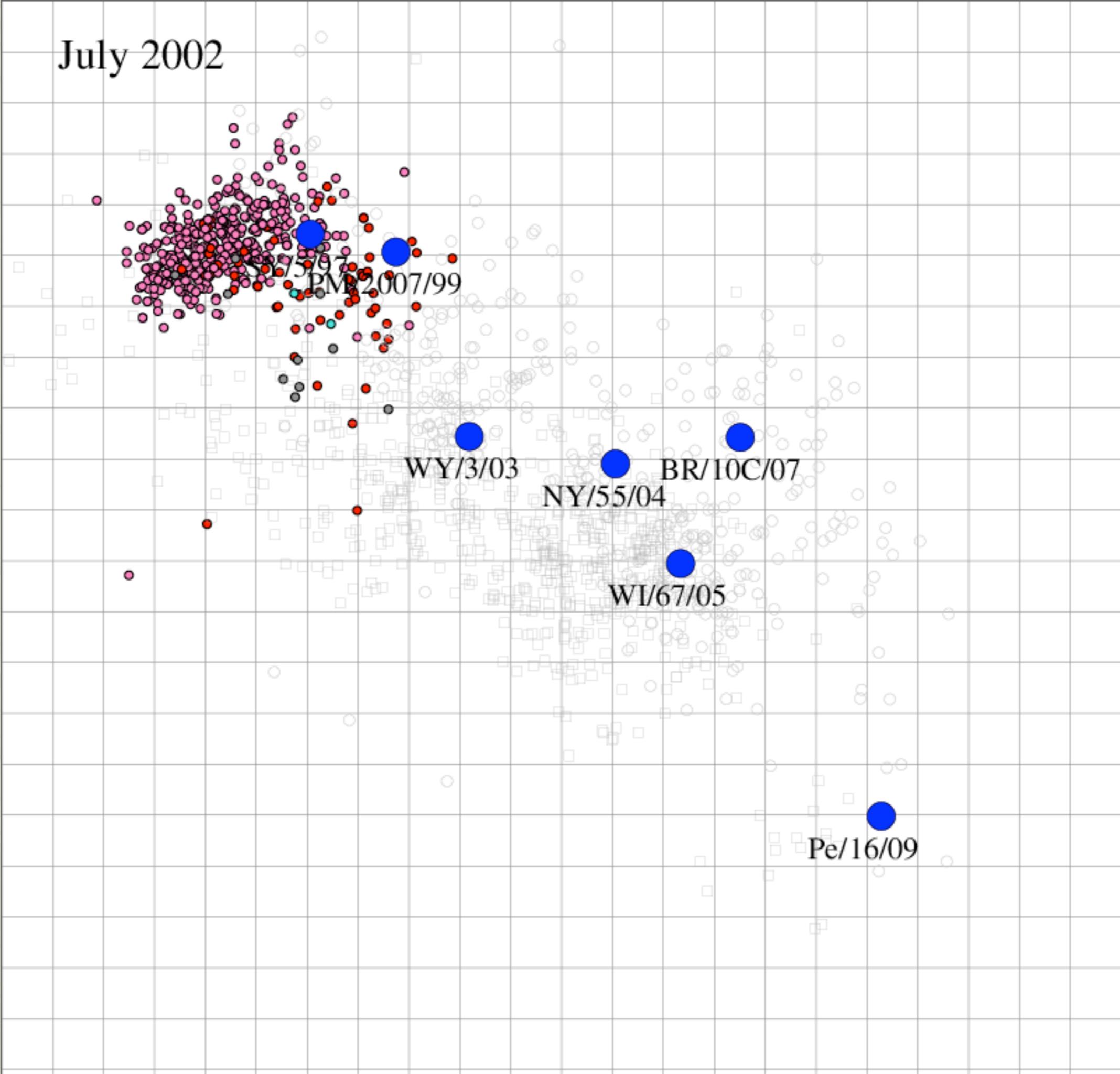
January 2002



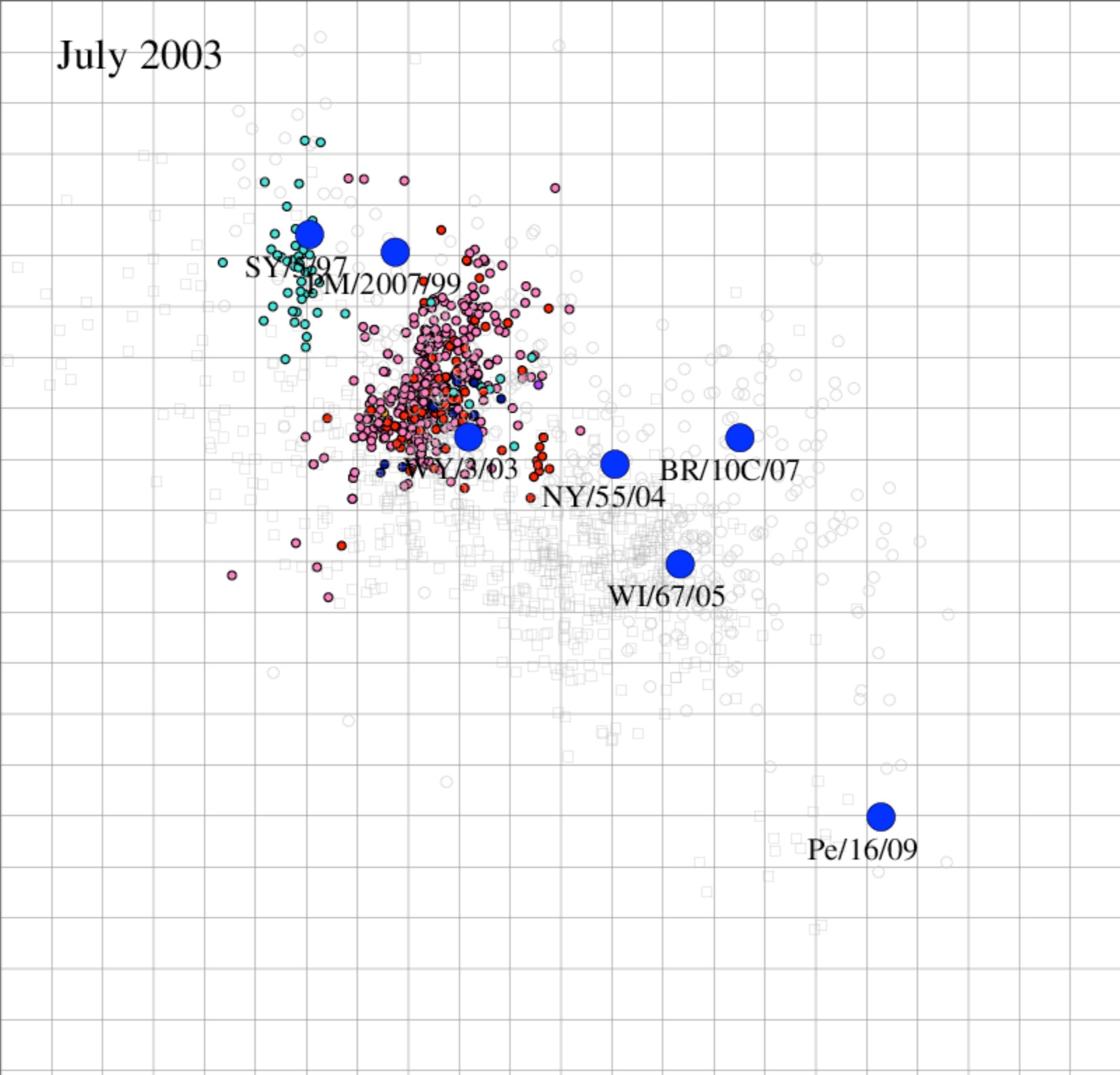
January 2002



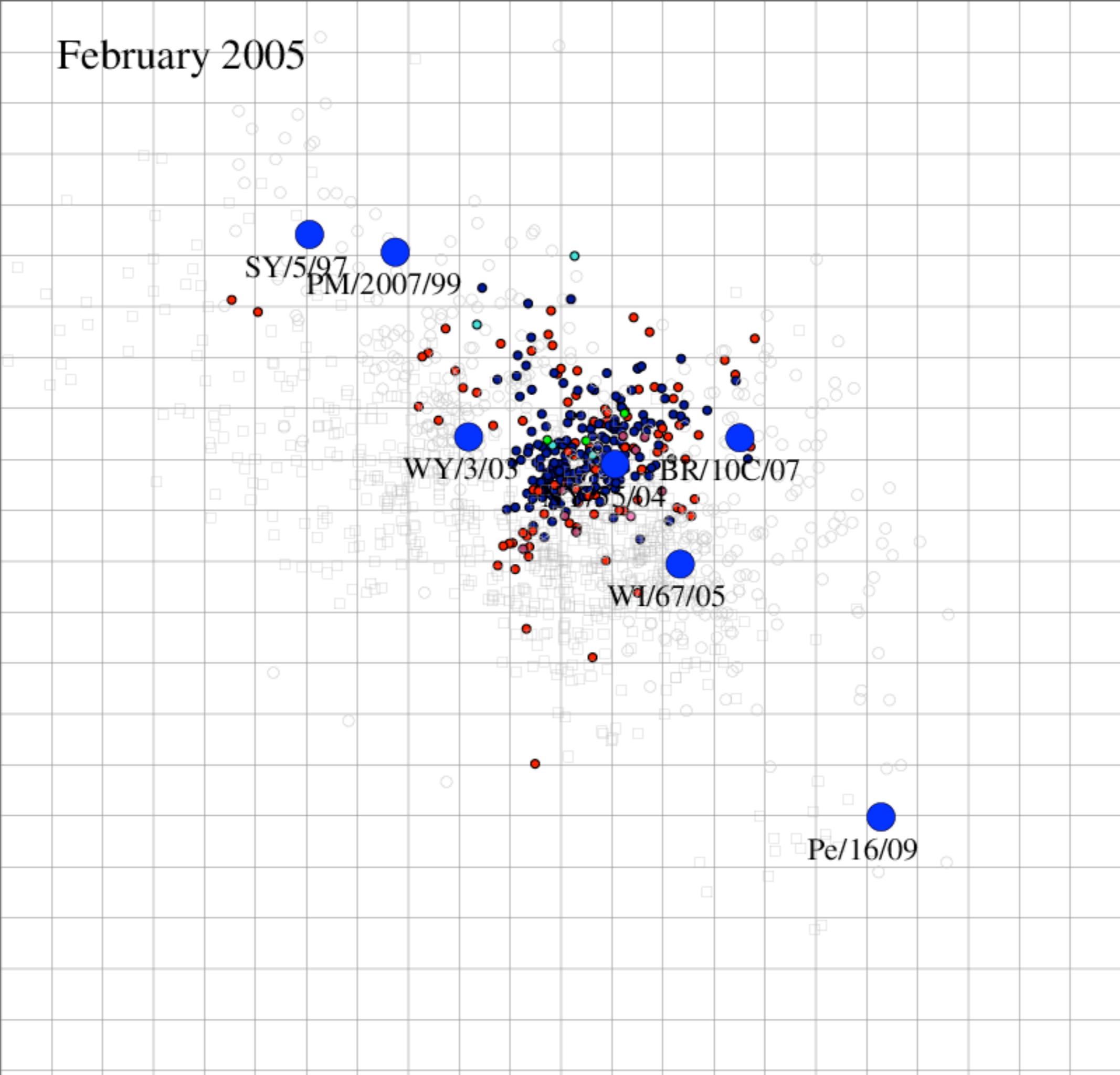
July 2002



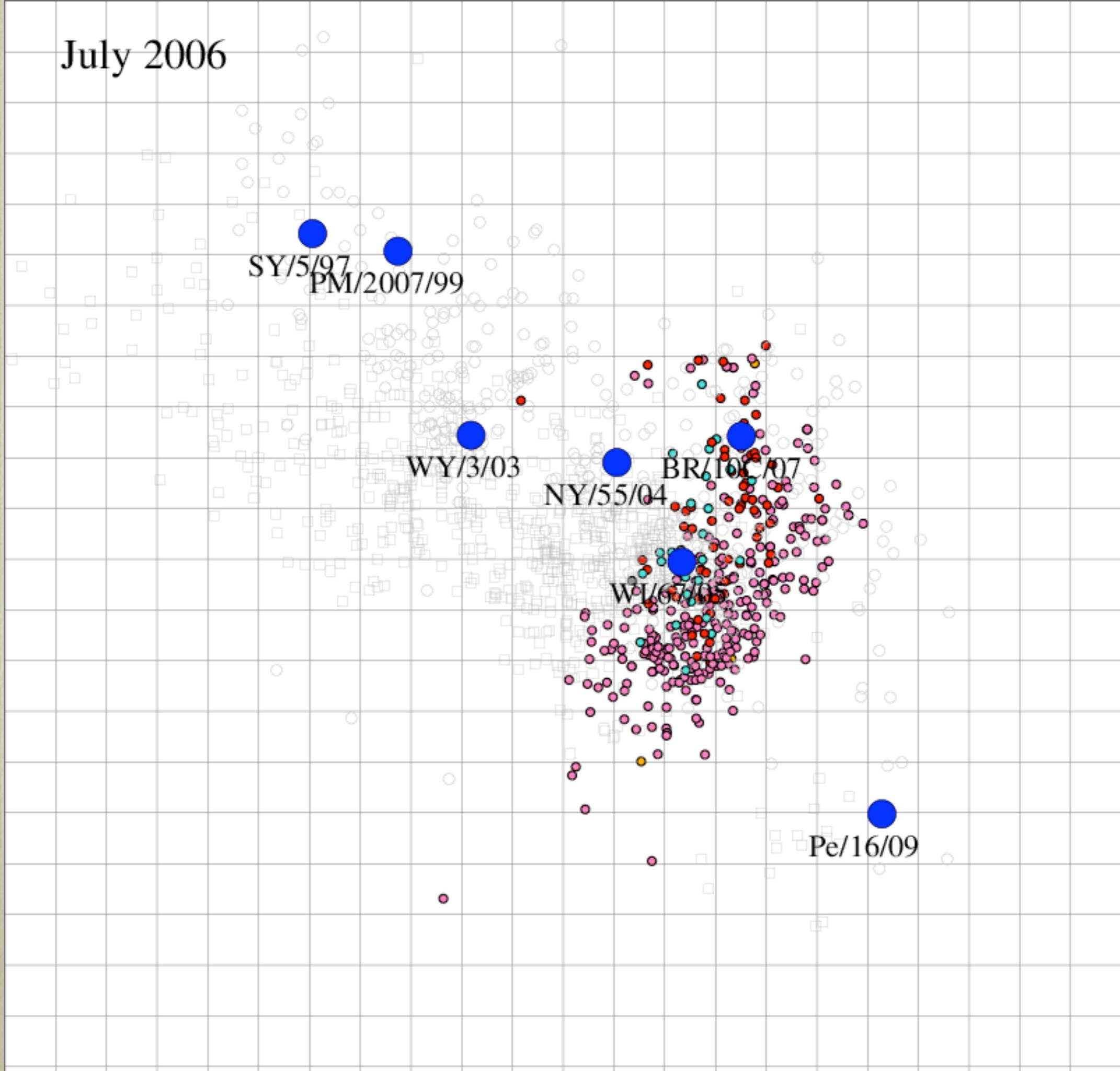
July 2003



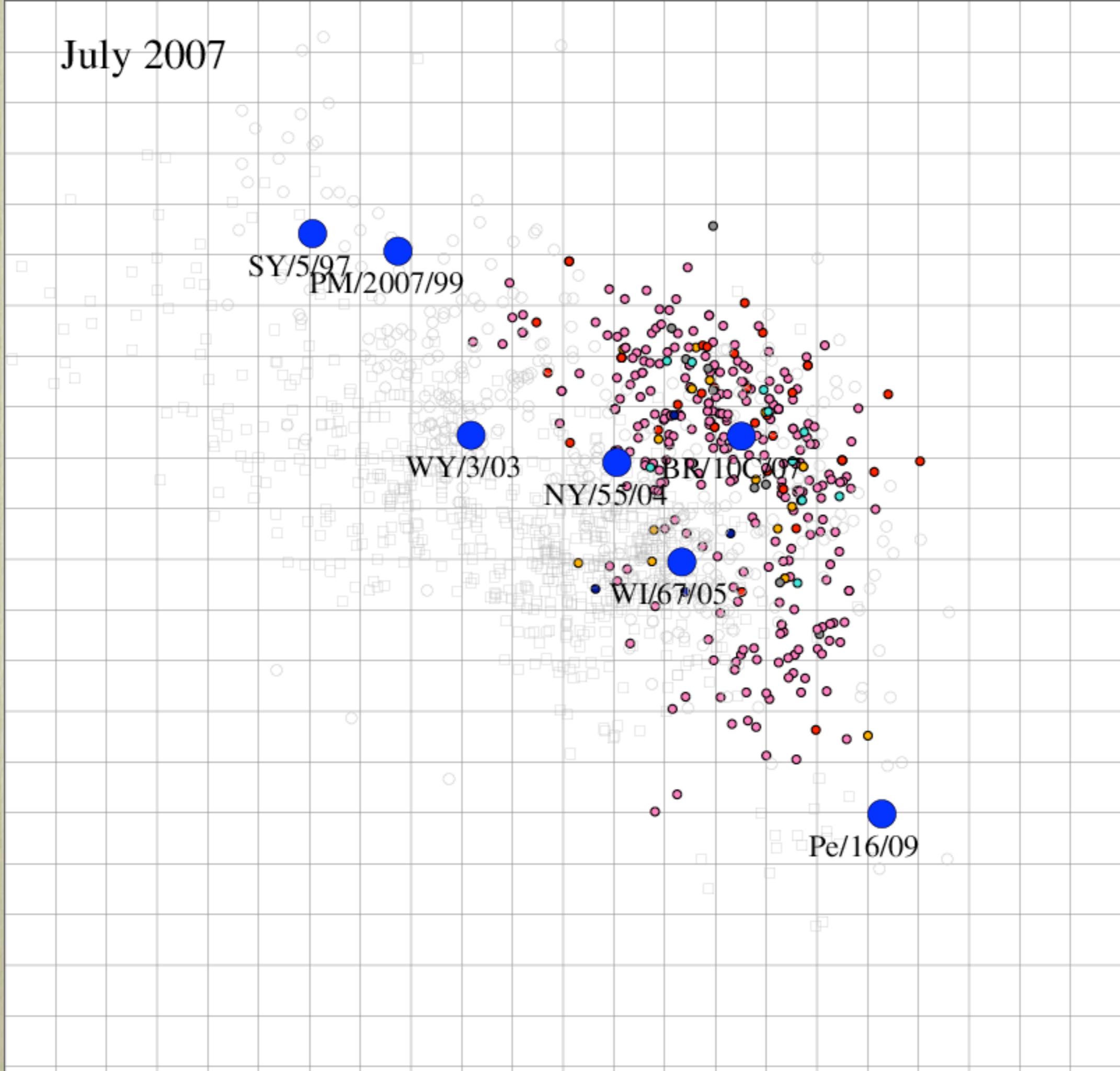
February 2005



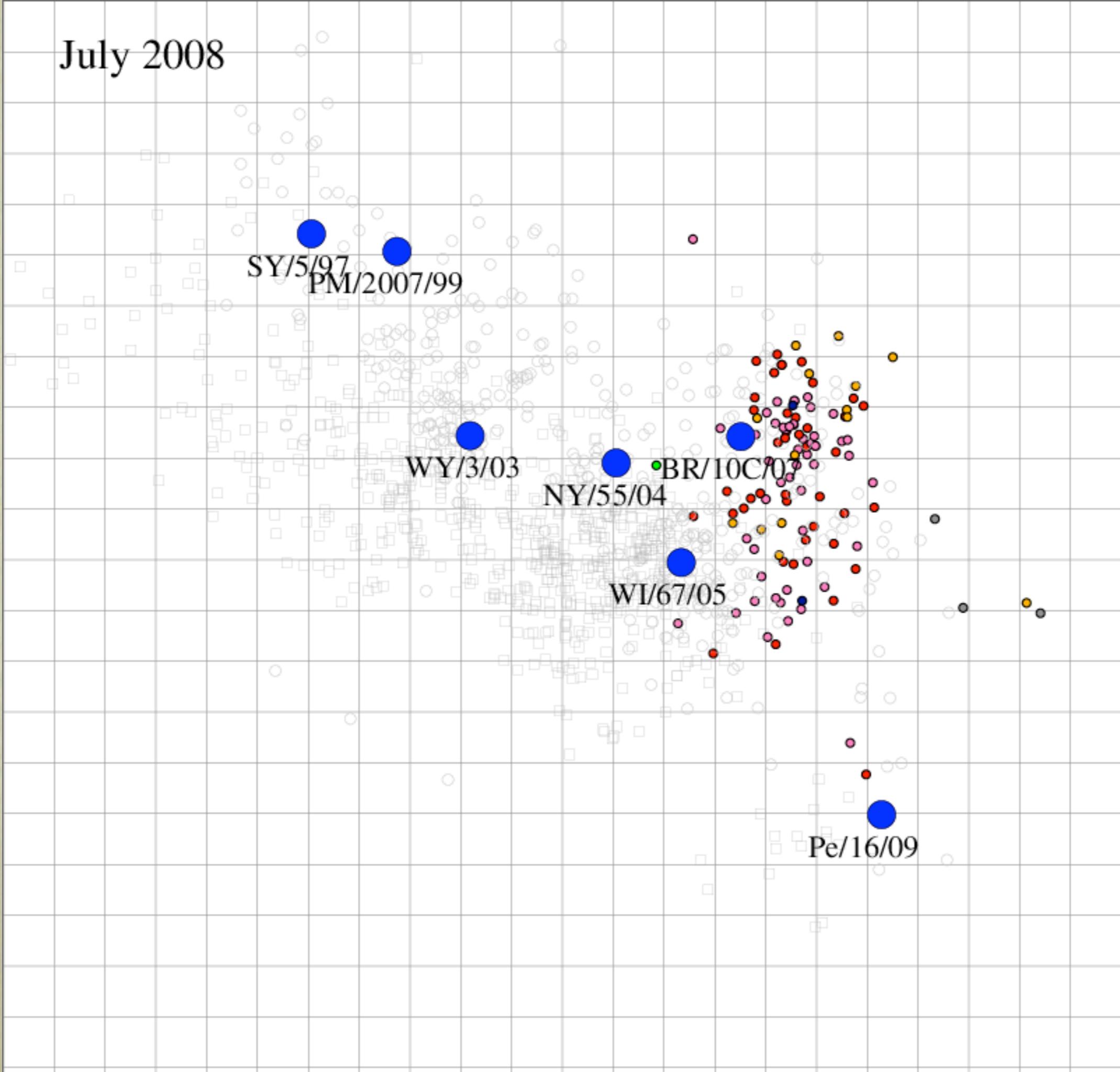
July 2006



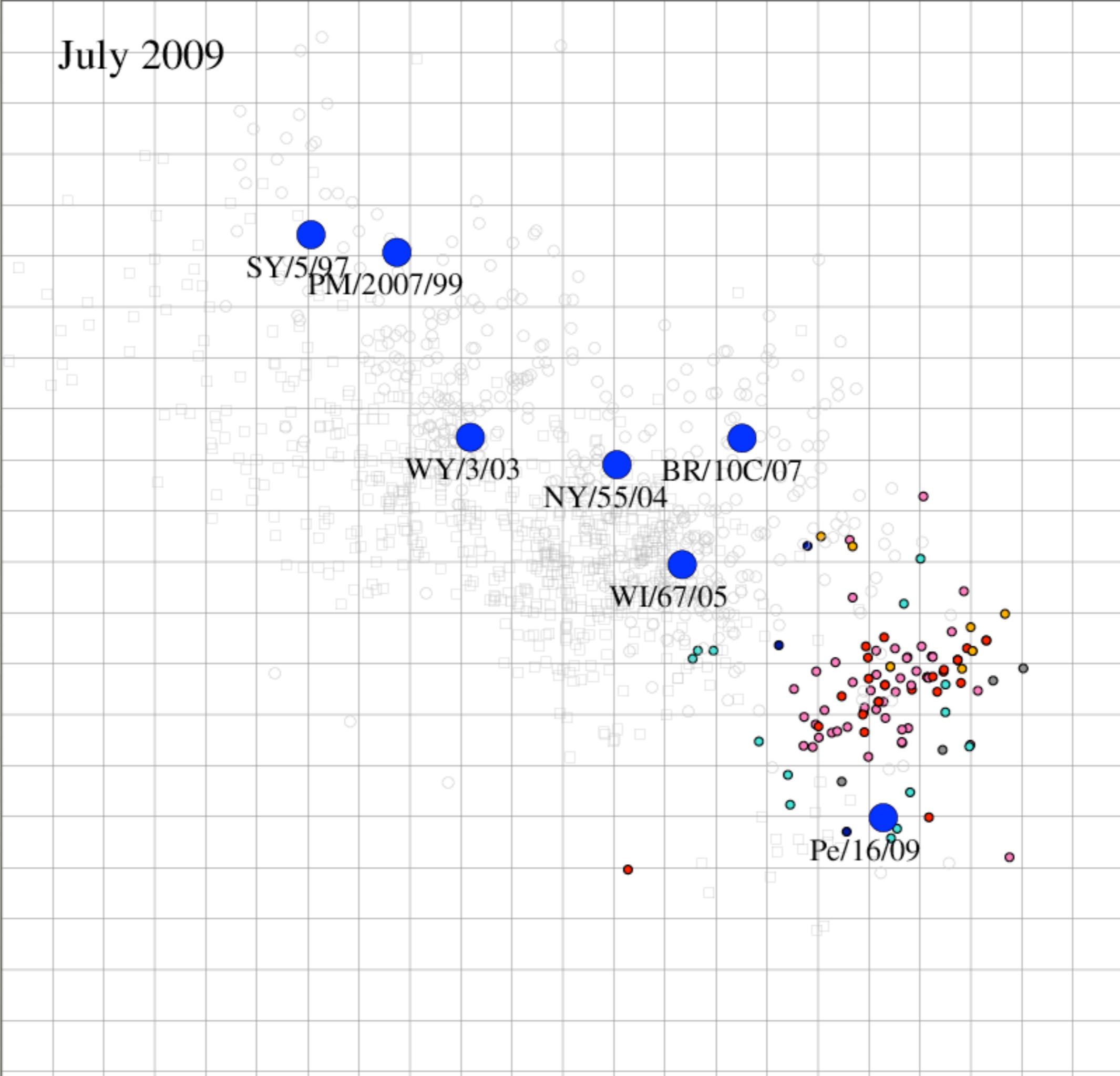
July 2007



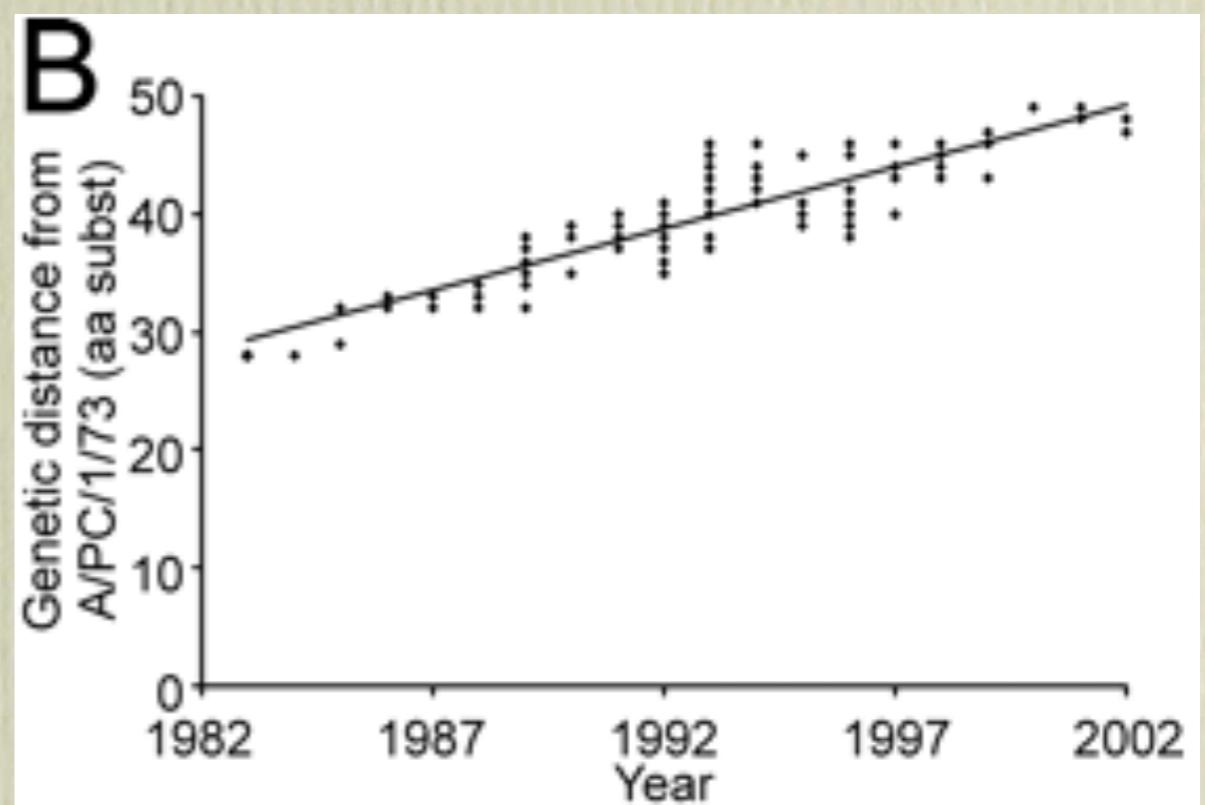
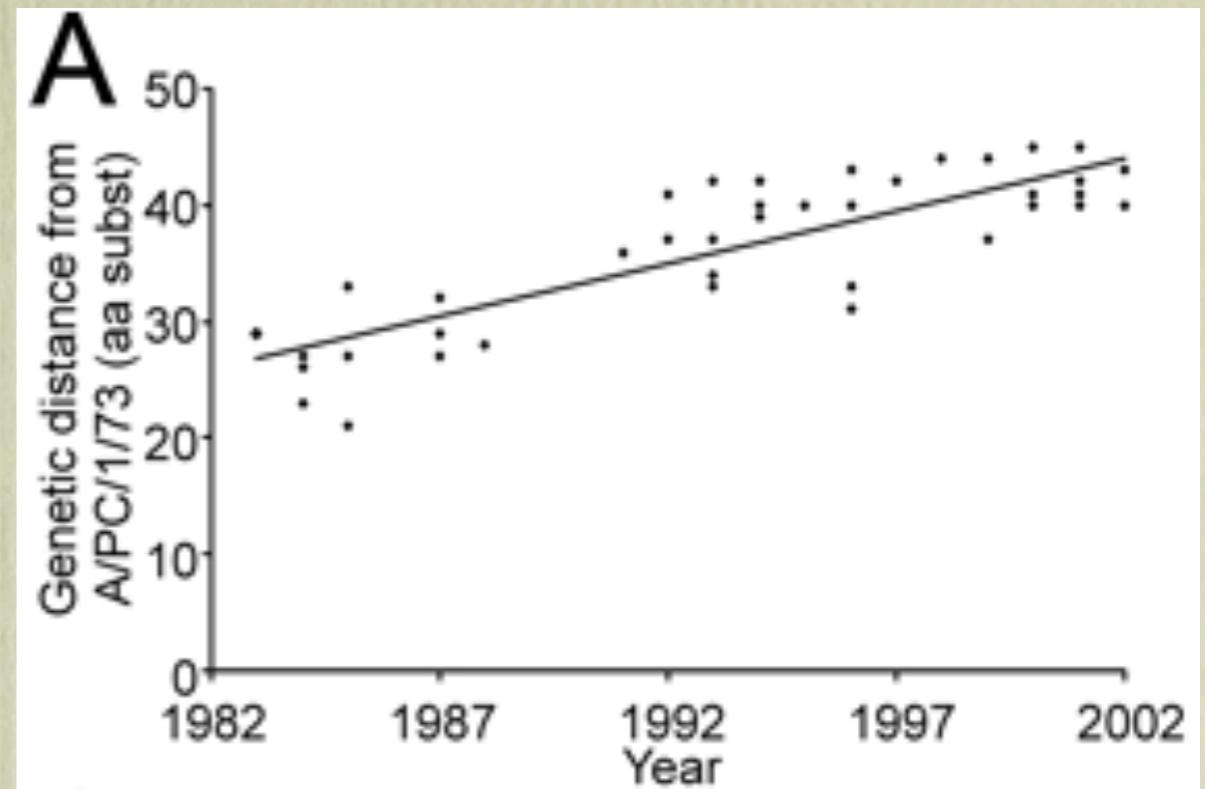
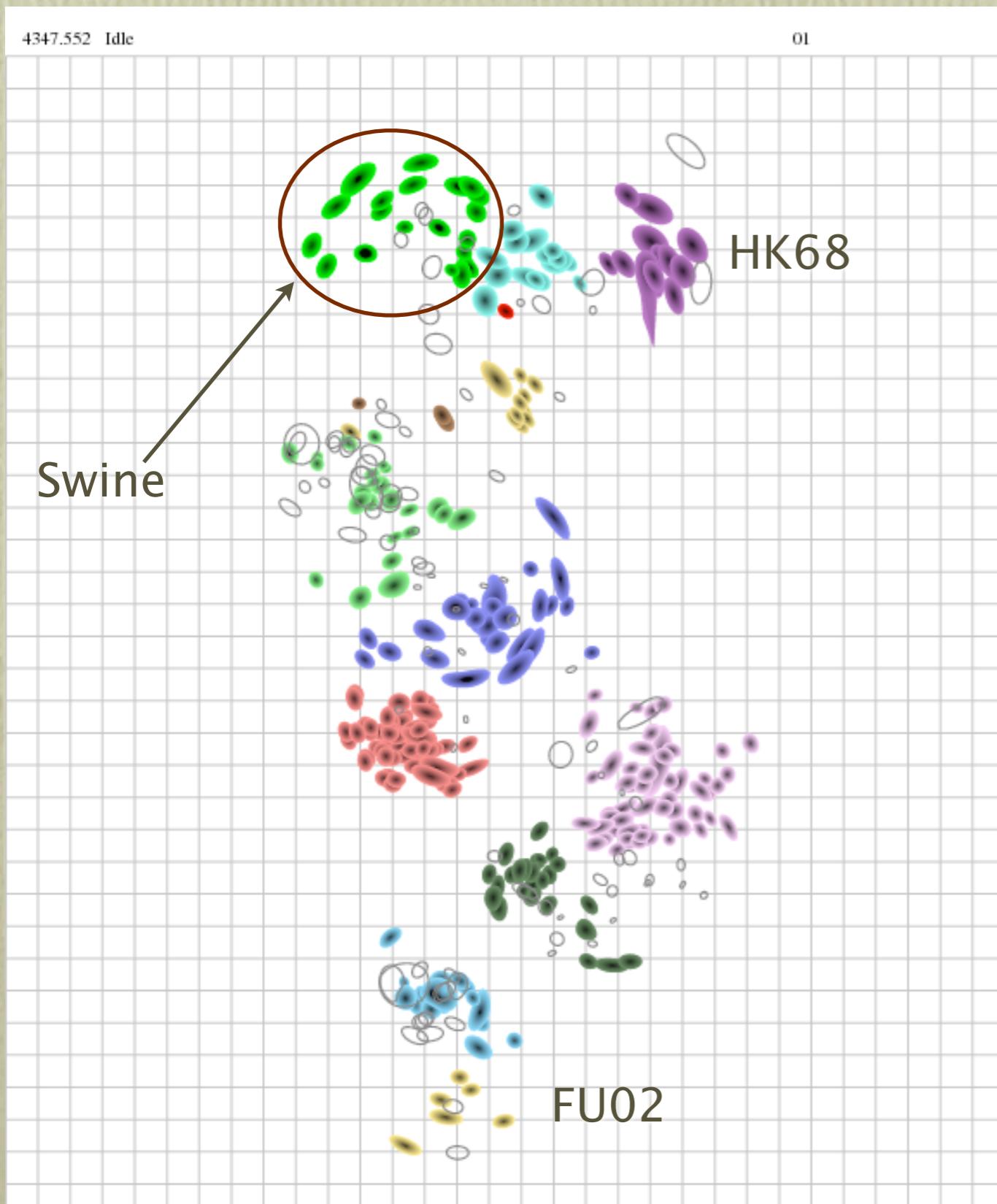
July 2008



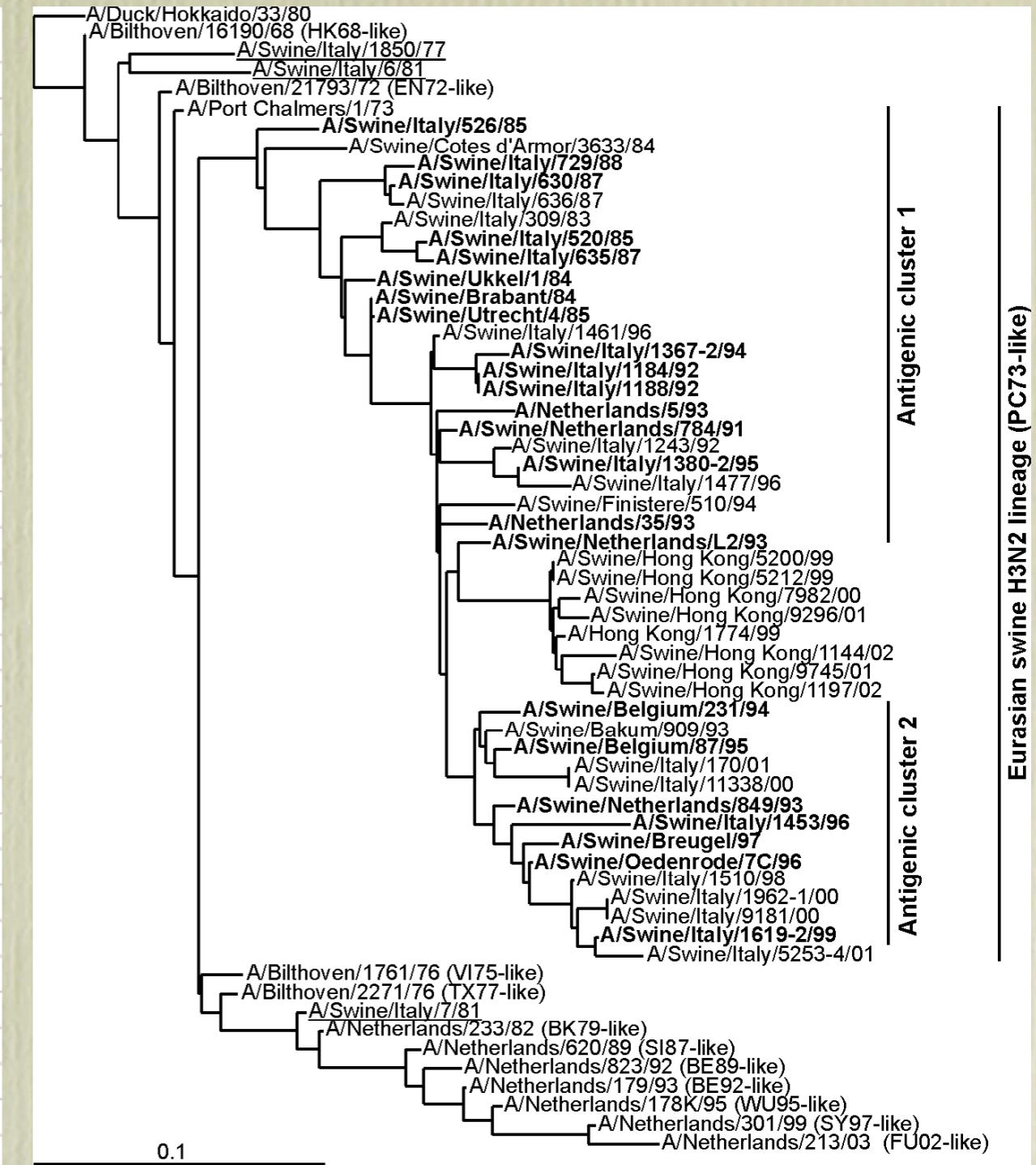
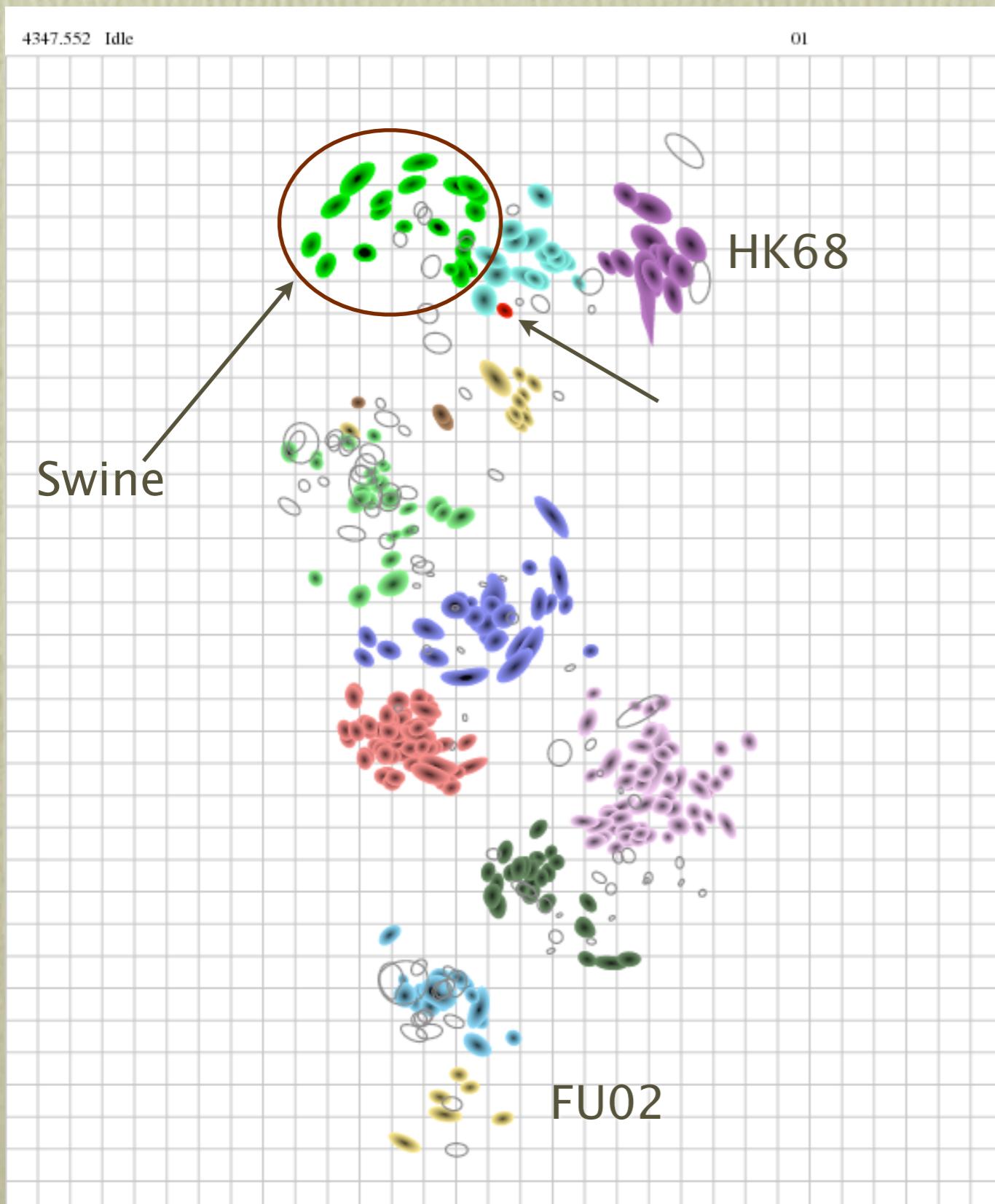
July 2009



Human & swine



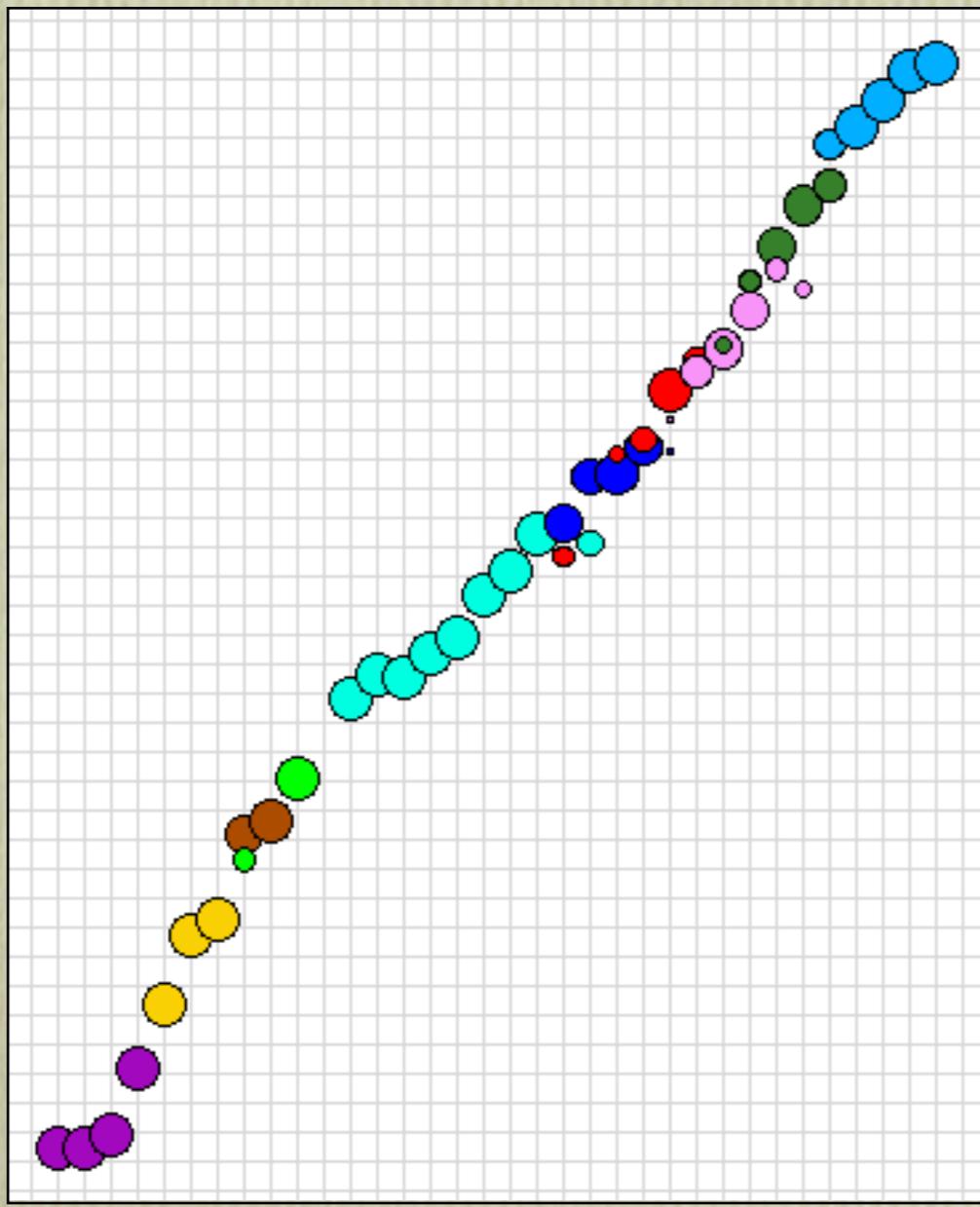
Human & swine



de Jong et al, J. Virol 2007

Genetic vs Antigenic

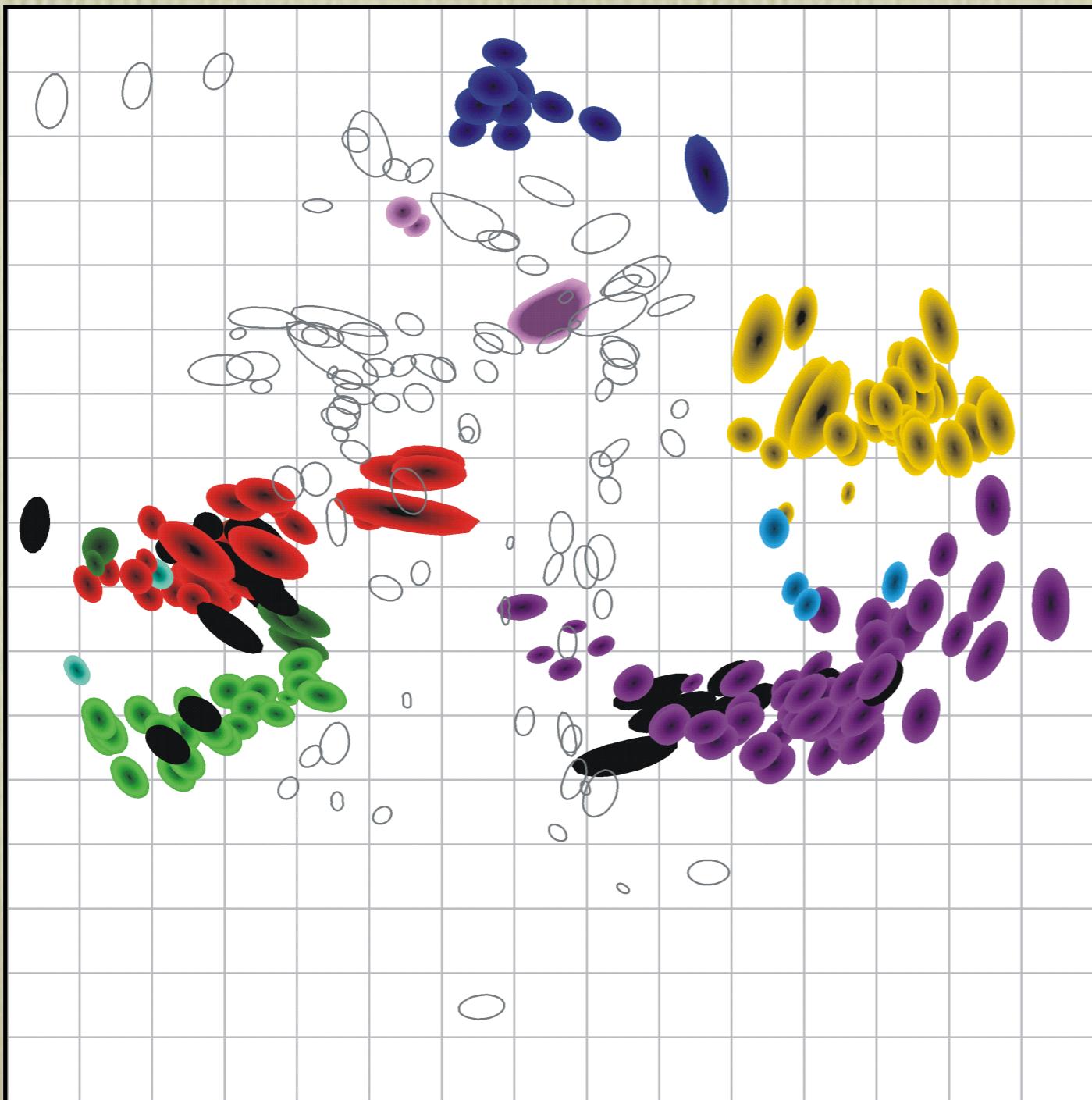
Distance from 1968 strain



Antigenic cartography is a general method

- Other influenza vaccine components (H1, B)
- Pandemic vaccines
- Influenza in other species (e.g., bird, horse, pig)
- Other diseases (e.g., dengue, norovirus)
- 12 years of practice

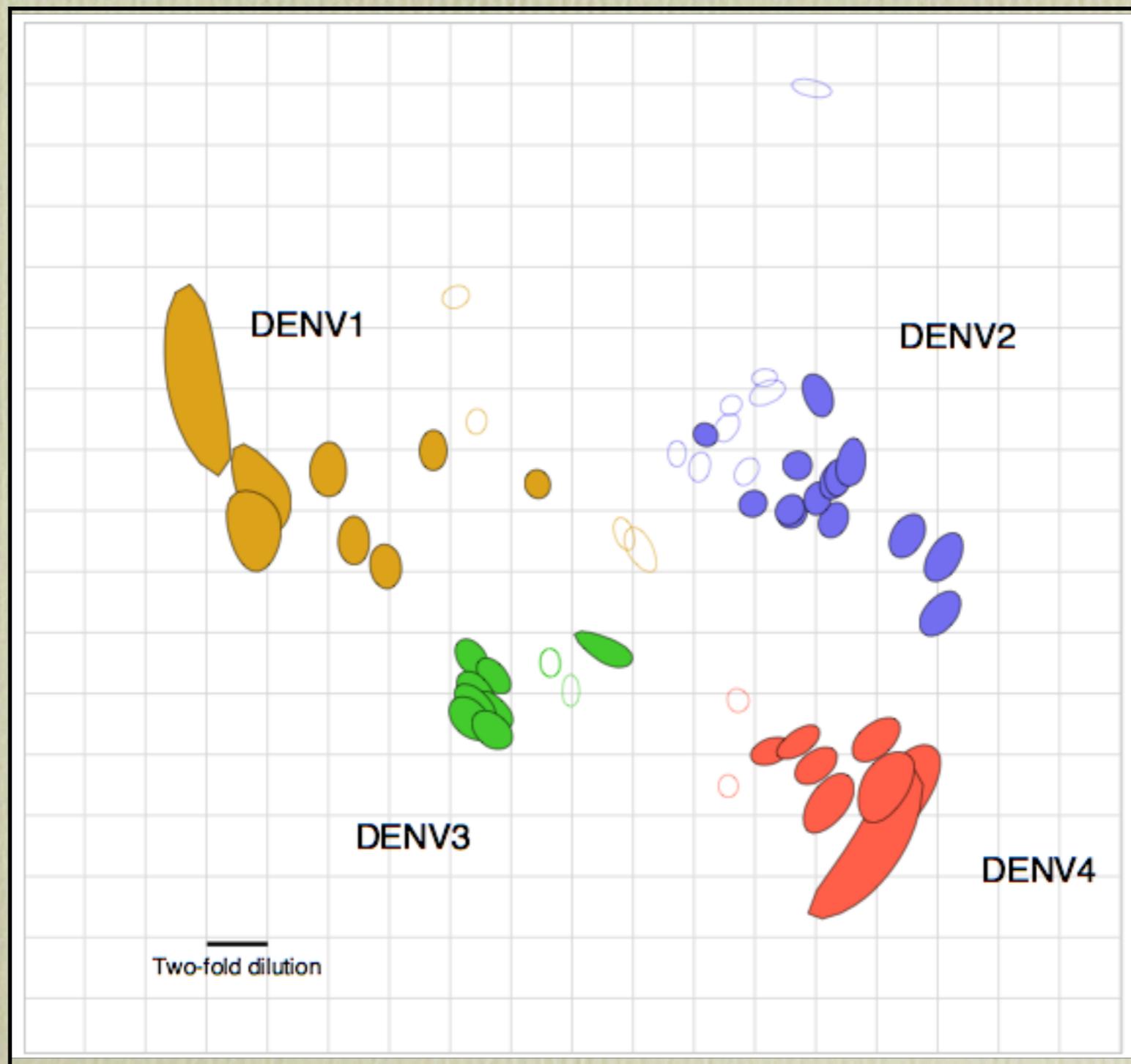
H5 map



Data from

- CDC
- St Jude
- Hong Kong U
- Erasmus MC

Dengue



4 Thanks

Acknowledgments

WHO global surveillance

CDC: Nancy Cox, Sasha Klimov, Michael Shaw

MELB: Ian Gust, Ian Barr, Aeron Hurt, Alan Hampson

NIID: Tashiro Masato, Takato Odagiri

NIMR: Alan Hay, Yi Pu Lin, Vicky Gregory

WHO: Wenqing Zhang, Klaus Stöhr

Funding

Santa Fe Institute

Erasmus Medical Centre, Viroscience Department

EU Framework 5 Novaflu, 6 Virgil, 7 Antigone & Emperie

NIH Director's Pioneer Award

Cambridge Infectious Disease Consortium

Acknowledgments

University of Cambridge (UK)

Derek Smith

Colin Russell

Nicola Lewis (& AHT)

Dan Horton (& VLA)

Ana Mosterín

Eugene Slepnev

Yan Wong (& Leeds)

David Burke

Margaret Mackinnon (& KEMRI)

Leah Katzelnick

Erasmus Medical Centre (NL)

Ron Fouchier

Ab Osterhaus

Jan de Jong

Bjorn Koel

Guus Rimmelzwaan

Walter Beyer

Theo Bestebroer

Ruud van Beek

Los Alamos National Laboratory (US)

Alan Lapedes