Heterogeneity in the Immune Response to Viruses

feature article

Mathematical adventures in biology

Michael W. Deem

A short personal tour of biological systems reveals the flavor and variety of biological questions amenable to illumination by mathematical analysis.

Michael W. Deem is a professor of physics and astronomy and the John W. Cox Professor in Biochemical and Genetic Engineering at Rice University in Houston, Texas.

The contemplation and resolution of questions at the interfaces of biology, mathematics, and physics promise to lead to a greater understanding of the natural world and to open new avenues for physics. The choice of questions in this article, most of them related to the statistical behavior of biological systems, reflects my own research interests. But it also reflects my belief that some of the unresolved issues in mathematical biology are related to the diversity, randomness, variation, and correlations in biology. With luck, physics-based approaches may shed further light on those issues.

The mathematical focus of the research questions I propose complements the public-health focus of the 14 Grand Challenges in Global Health announced in October 2003.[1] Those challenges have realigned health-related research priorities—not only those of the Bill & Melinda Gates Foundation, which initiated the identification of the challenges, but also those of other public and private research funding bodies. Several of the challenges concern the development of vaccines and drug treatments, topics that invite mathematical analysis.

The following are a few suggestions for mathematical adventures in biology. The first topic concerns the roles of localization, discreteness, and fluctuations in natural biological systems. Cells are not simply well-mixed test tubes, as evidenced by the role of fluctuations in a sense of life's processes. The second topic concerns a general question about the mechanism of evolution in biology. Mathematical results might quantify the probability of life as we know it and might be tested in laboratory evolution experiments. The last topic addresses a practical aspect of pathogen evolution. In this case, mathematical results might aid drug or vaccine design, or they might predict the likelihood of future epidemics or the emergence of new pathogens.

The answers to many if not all of the questions suggested in this article lie within the grasp of the physics and biology communities. The answers can be tested experimentally and in the interpretation of biological data, and have direct implications for medical practice. They may lead to a more thorough understanding of biology and in all likelihood will lead to an ever-expanding set of new questions.

The roll of fluctuations

From the cell to the organism, what role does fluctuation play in natural function? Cellular noise arising from the nonuniform distribution of biological molecules in the cell is now appreciated as an interesting physics problem.[2] Figure 1, for example, shows random variations that arise in the concentration of a protein due to stochastic variation of both the environment outside the cell and the biochemical reactions within a cell.

Many of the molecules of life, such as DNA, mRNA, and enzymes, are present at exceedingly low concentrations—from 1 to 100 molecules per cell.[3] At such low concentrations, the traditional equations of solution chemistry no longer apply and the stochastic fluctuations associated with the transport and reaction of individual molecules become apparent. At equilibrium, the thermodynamics is that of a small system (see the article by Carlos Bustamante, Jan Liphardt, and Felix Ritort, PHYSICS TODAY, July 2005, page 43). An important datum of biology is that many interesting reactions occur at finite times—that is, when equilibrium has not been established and when dynamics is important. Indeed, one of the differences between much of biology and traditional condensed-matter physics, which has provided useful techniques to the mathematics of biology, is the importance of finite time and finite population size.

A possible way to treat the random means that arises from reactions at low concentrations is to write a master equation for the process and map that equation onto a bosonic quantum field theory. To date, that approach has been pursued only for the simplest reactions. An alternative, approximate treatment uses mean-field theory but only in the regions of parameter space where at least one molecule is likely to be present; elsewhere the concentration is simply set to zero. The experiments shown in figure 1 could be described with such a theory, in combination with a description of the statistics of the random extracellular environment.

One might generally ask of biology, under what conditions does the integer constraint on the number of molecules or individuals matter? An integer constraint can induce correlations that traditional mean-field solution-chemistry theory would miss. And traditional theories of population evolution are mean field, so one might expect them to break down at the low concentrations that arise when new drug-resistant strains of bacteria evolve, as pathogens are eradicated, or when species are near extinction.

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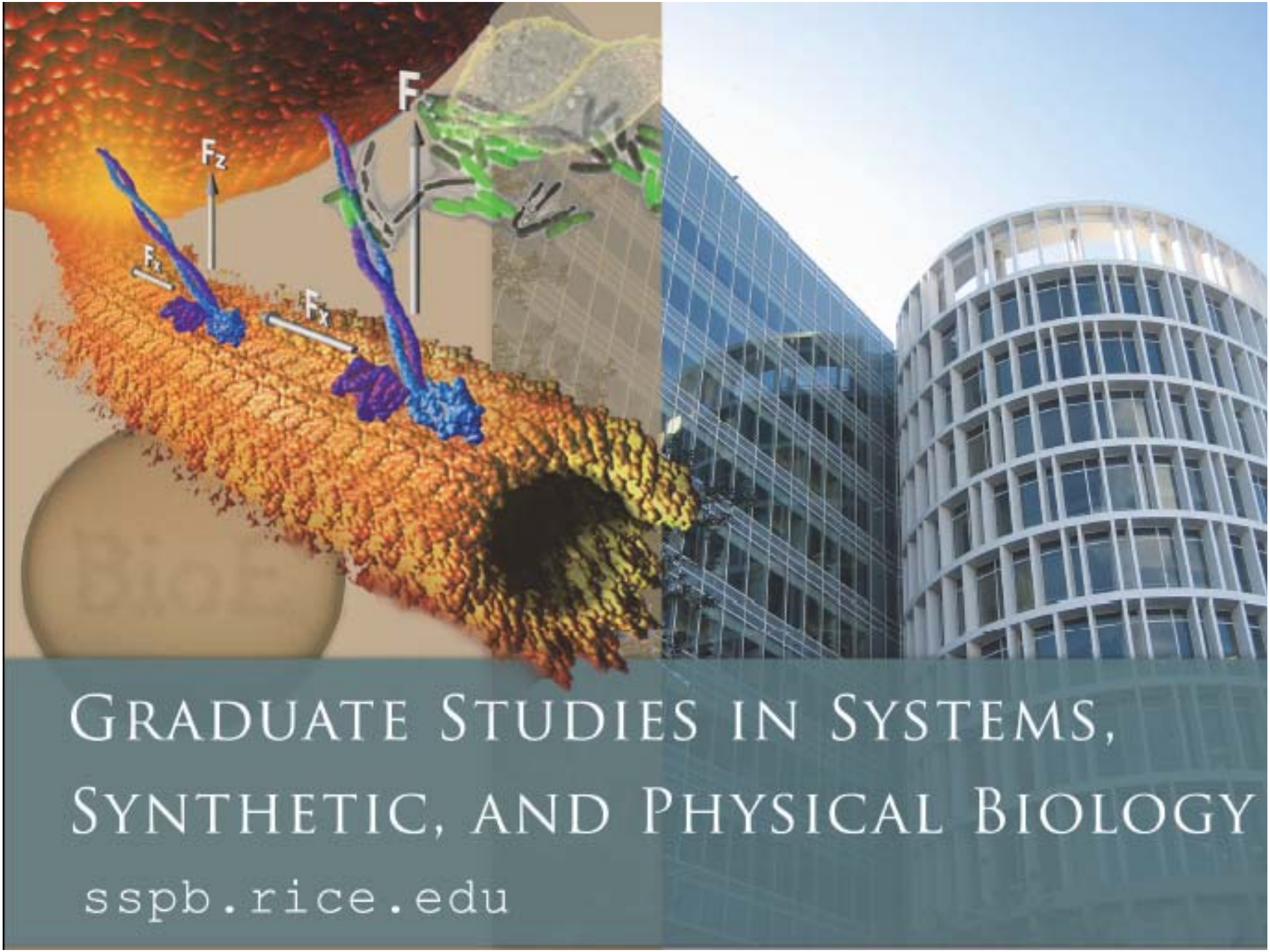
Outline

- Grand challenges in global health
- Dengue fever
- Virus evolution, H3N2 and H1N1
- The order parameter $p_{epitope}$
  (a new tool for vaccine design)
- Detection of new flu strains

Deem and Lee, *PRL* **91** (2003) 068101
Park and Deem, *Physica A* **341** (2004) 455
Gupta, Earl, and Deem, *Vaccine* **24** (2006) 3881
Zhou and Deem, *Vaccine* **24** (2006) 2451
Pan, Subieta, and Deem, **24** *PEDS* (2009) 291
J. Chem. Theory Comput. **7** (2011) 1259
J. Mol. Evol. **72** (2012) 90

BRC, Rice University



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Grand Challenges in Global Health

GOALS AND GRAND CHALLENGES

To improve childhood vaccines:

- GC 1: Create effective single-dose vaccines that can be used soon after birth;
- GC 2: Prepare vaccines that do not require refrigeration;
- GC 3: Develop needle-free delivery systems for vaccines.

To create new vaccines:

- GC 4: Devise reliable tests in model systems to evaluate live attenuated vaccines;
- GC 5: Solve how to design antigens for effective, protective immunity;
- GC 6: Learn which immunological responses provide protective immunity.

To control insects that transmit agents of disease:

- GC 7: Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population;
- GC 8: Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population.

To improve nutrition to promote health:

- GC 9: Create a full range of optimal bioavailable nutrients in a single staple plant species.

To improve drug treatment of infectious diseases:

- GC 10: Discover drugs and delivery systems that minimize the likelihood of drug-resistant microorganisms.

To cure latent and chronic infections:

- GC 11: Create therapies that can cure latent infections;
- GC 12: Create immunological methods that can cure chronic infections.

To measure disease and health status accurately and economically in poor countries:

- GC 13: Develop technologies that permit quantitative assessment of population health status;
- GC 14: Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point-of-care.

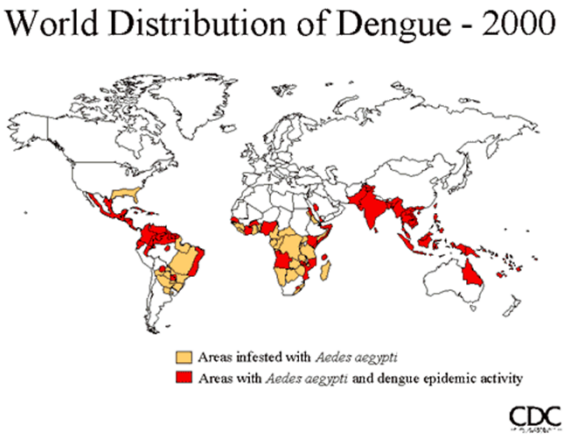
Bill Gates, World Economic Forum in Davos, Switzerland. Science and Technology: progress against disease.

H. Varmus *et al.*, *Science* **302** (2003) 398-399.

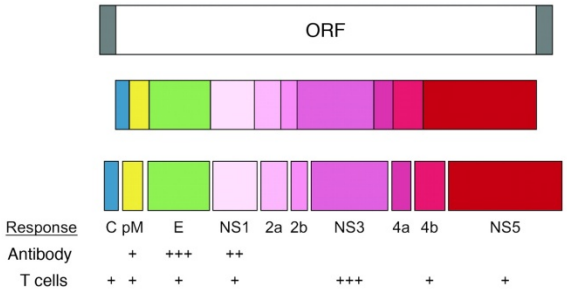
- To improve vaccines
- To create new vaccines

Theory of the Immune System

- Interested in fluctuations, correlations, diversity, randomness
- Immunodominance in dengue fever
- Influenza evolution and vaccine effectiveness



Dengue Fever

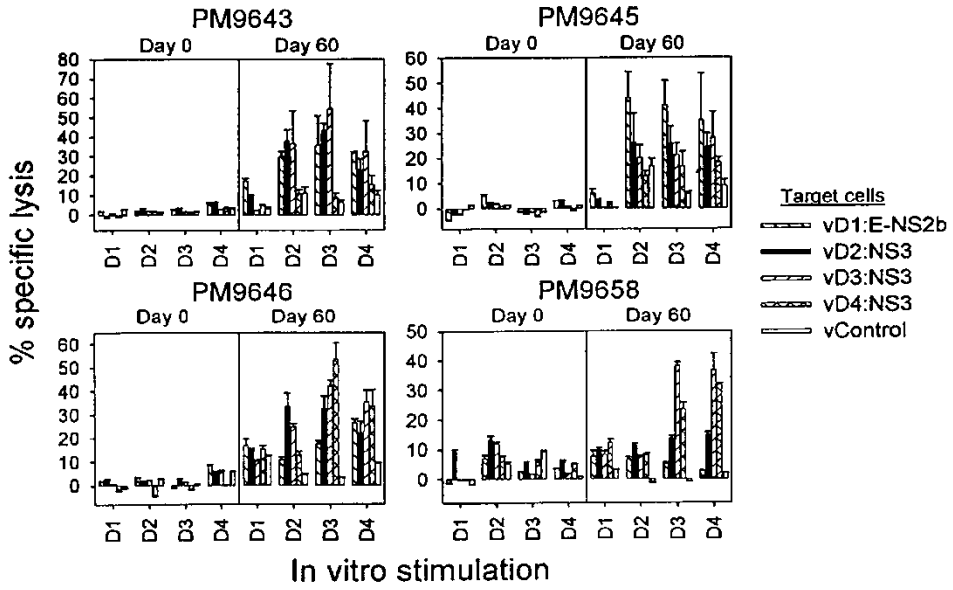


A. Rothman, Nat. Med. Rev.

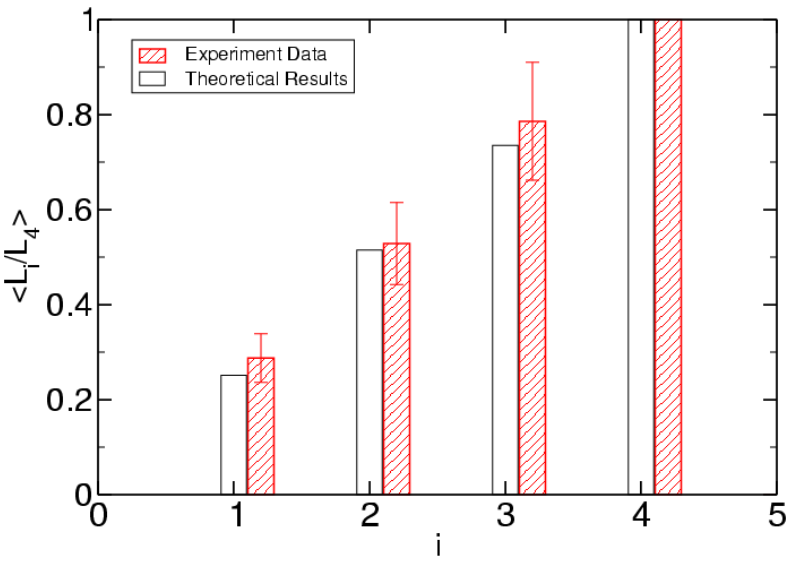
- The most important vector borne human virus *Clin. Microbiol. Rev.* **11** (1998) 480; *PNAS* **96** (1999) 7352; *Rev. Med. Virol.* **11** (2001) 301; *BMJ* **324** (2002) 1563; *Emer Themes Epidemiol.* **2** (2005) 1
- The most important mosquito-borne virus in 2005 (CDC, WHO)
- Transmitted by Aedes aegypti and
- A. albopictus mosquitos
- 2.5 Billion people live in 100 countries affected
- 50-100 million people infected each year
- 500 000 cases of dengue hemorrhagic fever
- 24 000 yearly human mortality

Dengue fever: Immunodominance

- 4 serotypes of dengue fever, 1 conservative mutation between each pair of strains
- Most important vector-borne human virus
- Immunodominance inhibits tetravalent vaccine



Rothman *et al.*, *Vaccine* **19** (2001) 4694



Park and Deem, *Physica A* **341** (2004) 45
Zhou and Deem, *Vaccine* **24** (2006) 245

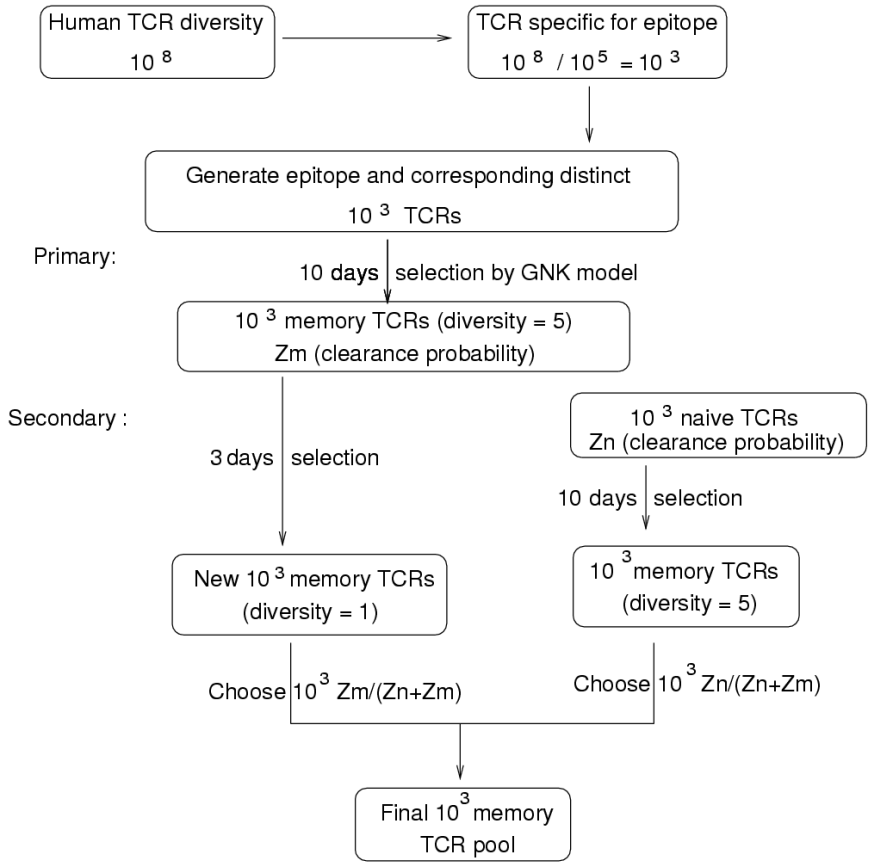
The T Cell Muturation Process

- Roughly 2.4×10^7 sequences in naïve repertoire, copy number 2.4×10^4
- T cell maturation is driven by cycles of concentration expansion
- Concentration increases 10^3 over 10 days
- Diversity of evolved sequences is 0.5% of initial, copy number 2×10^6

  T. P. Arstila *et al.*, *Science* **286** (1999) 958
- Theoretical total diversity 10^{11}
- 1 in 10^5 sequences bind any particular antigen

T Cell Maturation Process: Primary Response

- 10 rounds of selection with x = 58%
- Repertoire size N_{size} = 1000
- Leads to 10^3 concentration expansion and 0.5% diversity
- These cells become memory T cells (90% die)



Park and Deem, *Physica A* **341** (2004) 455

The Physical Model: Generalized NK (Spin Glass) Model

S. Kauffman and S. Levin, *J. Theor. Biol.* **128** (1987) 11
S. A. Kauffman and W. G. MacCready, *J. Theor. Biol.* **173** (1995) 427
A. S. Perelson and C. A. Macken, *Proc. Natl. Acad. Sci. USA* **92** (1995) 9657
L. D. Bogarad and M. W. Deem, *Proc. Natl. Acad. Sci. USA* **96** (1999) 2591

$$U = \sum_{i=1}^{M} U_{\alpha_i}^{\mathrm{sd}} + \sum_{i>j=1}^{M} U_{ij}^{\mathrm{sd-sd}} + \sum_{i=1}^{M} U_{i}^{\mathrm{pep-sd}} + \sum_{i=1}^{N_\mathrm{b}} \sum_{j=1}^{N_\mathrm{CON}} U_{ij}^{\mathrm{c}}$$ M=6, N_b=3, N_{CON}=3

$$U_{\alpha_i}^{\mathrm{sd}} = \frac{1}{\sqrt{M(N-K+1)}} \sum_{j=1}^{N-K+1} \sigma_{\alpha_i}(a_j, a_{j+1}, \cdots, a_{j+K-1})$$

N=9, K=4, L=5
Gaussian σ

$$U_{ij}^{\mathrm{sd-sd}} = \sqrt{\frac{2}{DM(M-1)}} \sum_{k=1}^{D} \sigma_{ij}^{(k)}(a_{j_1}^{(i)}, \cdots, a_{j_{K/2}}^{(i)}; a_{j_{K/2+1}}^{(j)}, \cdots, a_{j_K}^{(j)})$$

$$U_{i}^{\mathrm{pep-sd}} = \sqrt{\frac{1}{DM}} \sum_{k=1}^{D} \sigma_{i}^{(k)}(a_{j_1}^{\mathrm{pep}}, \cdots, a_{j_{K/2}}^{\mathrm{pep}}; a_{j_{K/2+1}}^{(i)}, \cdots, a_{j_K}^{(i)})$$

$$U_{ij}^{\mathrm{c}} = \frac{1}{\sqrt{N_\mathrm{b} N_\mathrm{CON}}} \sigma_{ij}(a_{j_1}^{\mathrm{pep}}, a_{j_2})$$

D=2

Park and Deem, *Physica A* **341** (2004) 455

How are T Cells Selected?

- Naïve $\rightarrow$ Activated $\rightarrow$ Memory
- Concentration changes $1 \rightarrow 10^3 \rightarrow 10^2$
- Diversity changes $10^3 \rightarrow 5$
- Stochastic selection for better binding constants *J. Immunol.* **165** (2000) 6081; *J. Exp. Med.* **189** (1999) 701; *J. Exp. Med.* **188** (1998) 71;

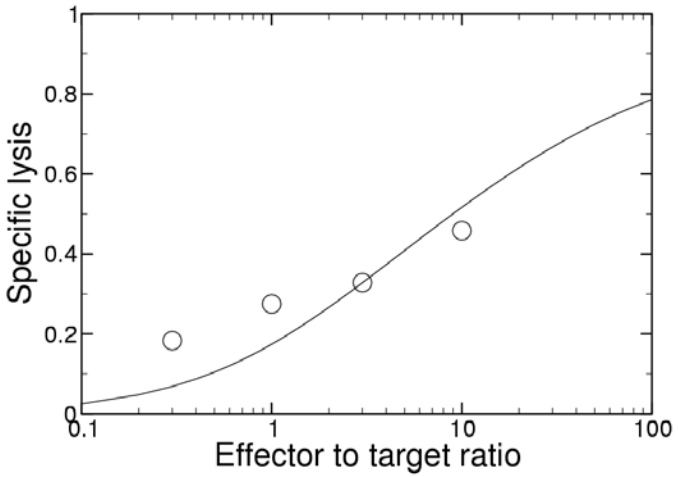
Nature Immunol. **3** (2002) 9; *Nature Immunol.* **3** (2002) 27; *Curr. Opin. Immunol.* **15** (2003) 120.

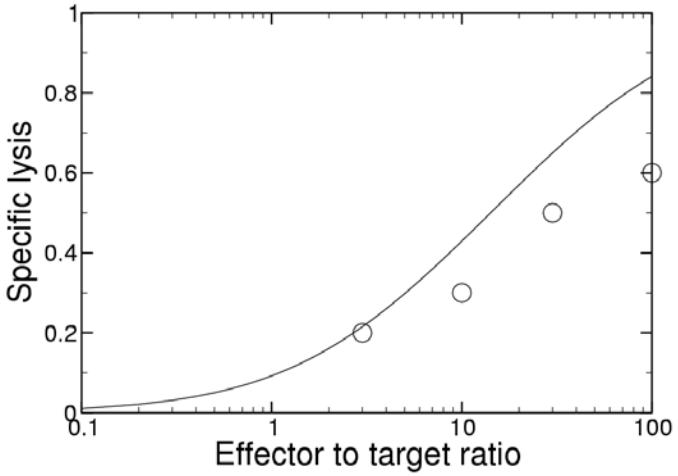
Specific Lysis: Conservatively Altered Peptides

- Measured for LCMV in mice
- LCMV strongly immunogenic: all memory cells are specific for LCMV
- *In vitro* and *ex vivo* response

J. Immunol. **157** (1996) 2358; *Nature* **394** (1998) 482

- *In vitro* > e*x vivo* because memory response is better than naïve response for peptides altered by one amino acid





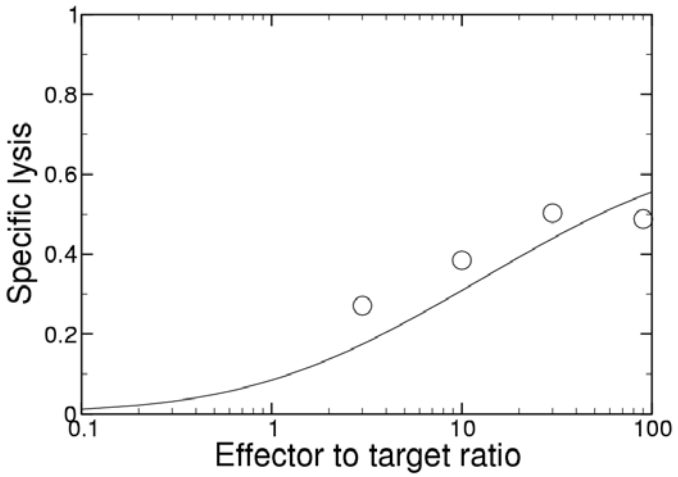
Park and Deem, *Physica A* **341** (2004) 455

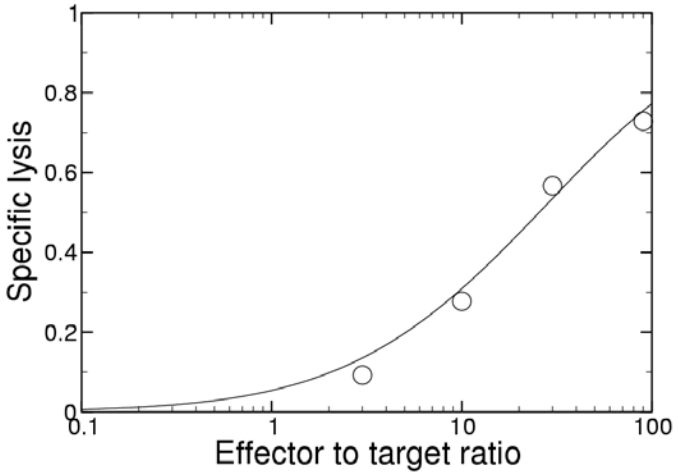
Specific Lysis: Non-Conservatively Altered Peptides

- *In vitro* and e*x vivo* response

Eur. J. Immunol. **28** (1998) 3110
J. Virol. **71** (1997) 5764

- Conservative slightly superior to non-conservative because conservatively altered peptide is more similar to the original peptide against which T cells evolved





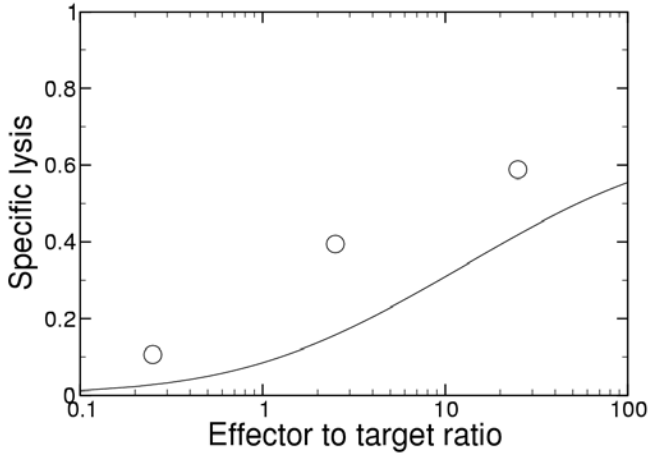
Park and Deem, *Physica A* **341** (2004) 455

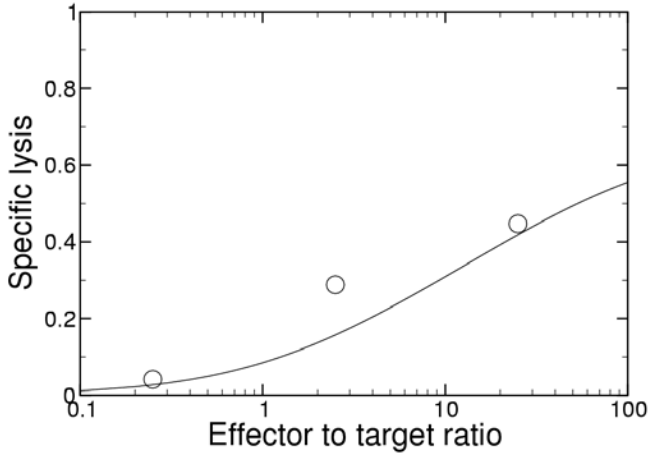
Human Disease APL

- APLs that occur in disease can inhibit the immune response
- This is thought to be a big problem
- E.g. human leukemia virus type I

Proc. Natl. Acad. Sci. USA **92** (1995) 4036

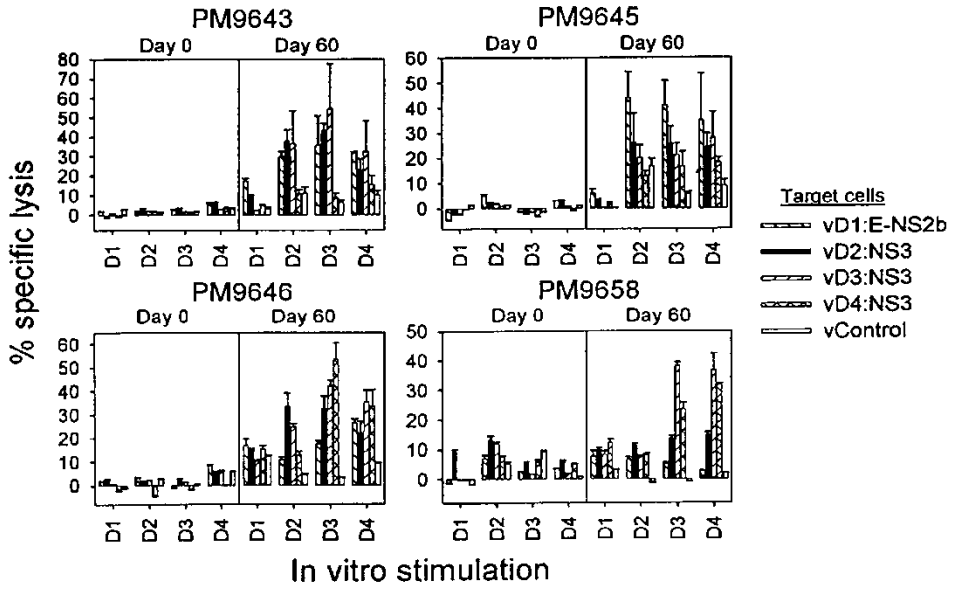
- 11 L $\rightarrow$ A (left) and 15 Y $\rightarrow$ A APLs (right)



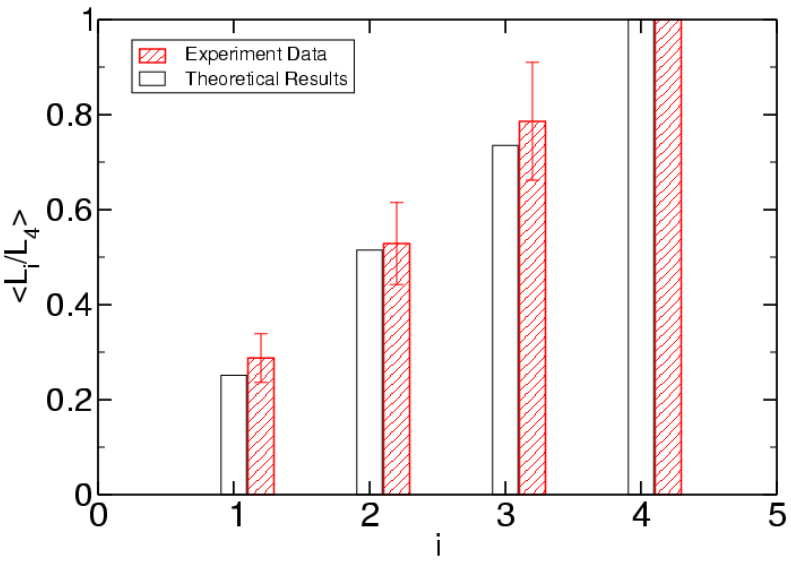


Dengue fever: Immunodominance

- 4 serotypes of dengue fever, 1 conservative mutation between each pair of strains
- Most important vector-borne human virus
- Immunodominance inhibits tetravalent vaccine



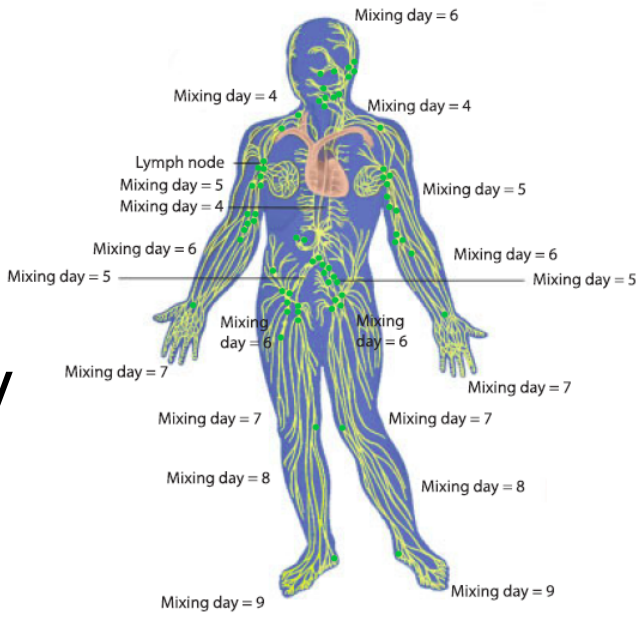
Rothman *et al.*, *Vaccine* **19** (2001) 4694

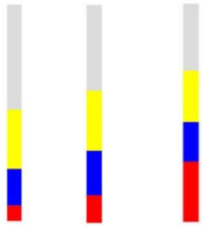


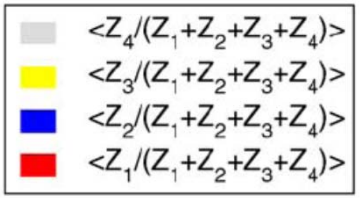
Park and Deem, *Physica A* **341** (2004) 45
Zhou and Deem, *Vaccine* **24** (2006) 245

Multisite Vaccination

- Humans have hundreds of lymph nodes
- T cells take 4-5 days to leave lymph nodes in large numbers
- Vaccination so that antigen is presented in physiologically distinct lymph nodes
- 2-4x improvement in uniformity of response







Experimental Verification

- Two studies investigated the diversity of a CD8T cell response to a mixture of HIV epitopes.
- In [1], mice were immunized with a mixture of AL11 and KV9 Db-restricted HIV epitopes. Injection to the same site resulted in a specific response to the KV9 epitope. Anatomic separation between injection sites resulted in a response against both epitopes.
- In [2], whether a broad CD8 T cell response recognizing multiple HIV-1 clades could be induced by a multi-component vaccine was assessed in mice. Single-clade A, B, and C vaccines generated limited cross-clade reactivity. Combining the three clades into one vaccine resulted in a reduced breadth of response due to immunodominance. Simultaneous administration of individual clade-specific vaccines into anatomically distinct sites on the body alleviated immunodominance and increased the number of epitopes recognized by the T cell response.
- In [3], a broader immune response to the 4-component vaccine was generated in moneys by multi-site than by single-site vaccination
- Sanofi-Pasteur dengue vaccine [4].

- 1) *J. Virol.*, 80:11991–11997, 2006.
- 2) *Eur. J. Immunol.*, 37:1–12, 2007.
- 3) AJTMH, 80:302-311, 2009.
- 4) US patent #7,718,358

A Theory of Epitopic Variation

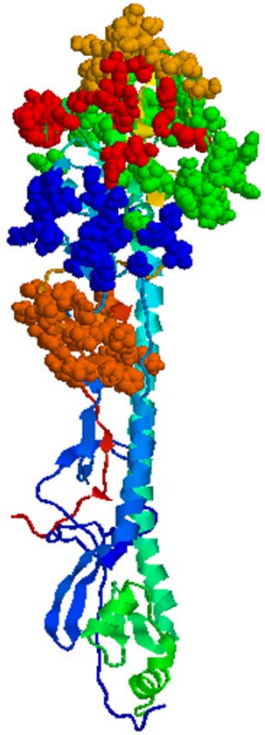
- Which amino acids will change as influenza escapes from the immune system?
  - Primarily those in the epitope of HA
- How can we predict which these will be?
  - r_i α -ΔA
  - Free energy calculations from statistical mechanics

$$Q_{\text{chain}}(N,V,T) = \frac{1}{N!}\int \mathrm{d}\mathbf{q}^N \sum_{\boldsymbol{\Gamma}_1,\ldots,\boldsymbol{\Gamma}_N} \exp\left[-\beta U\left(\mathbf{q}^N,\boldsymbol{\Gamma}^N\right)\right]$$

$$\Delta F_{ex}(l \to l+1) \equiv \mu_{ex}^{incr}(l \to l+1)$$

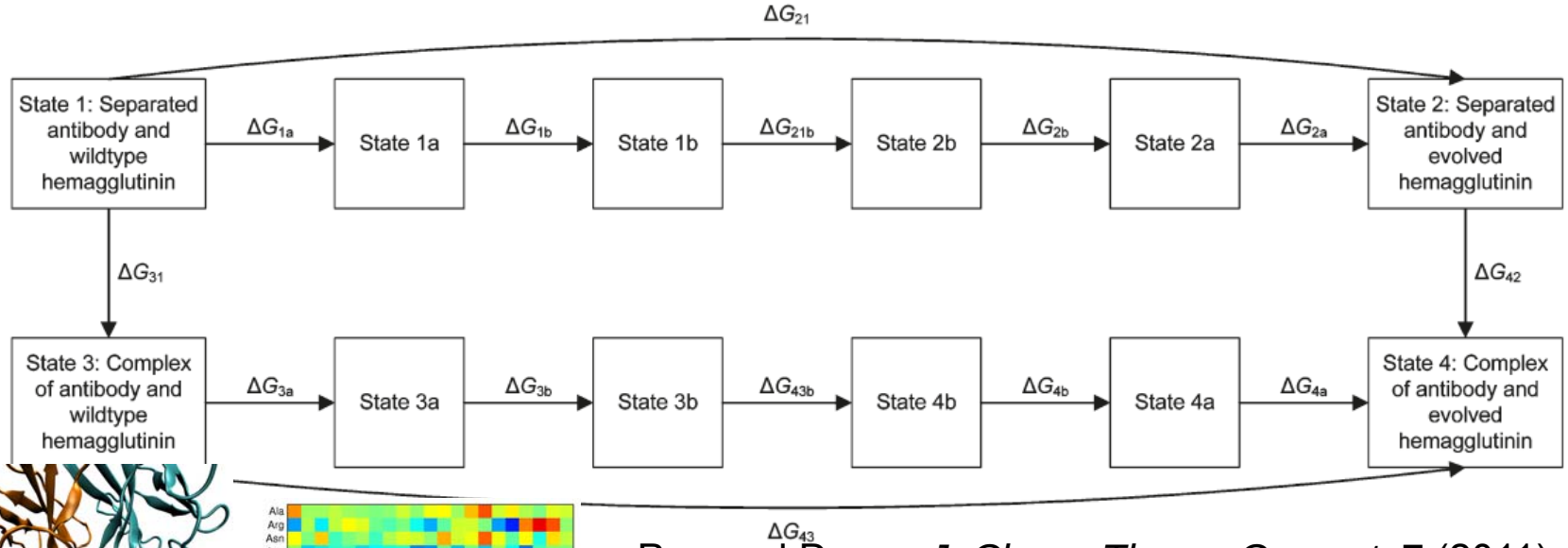
$$= -k_B T \ln\left\langle \exp\left[-\beta \Delta U(l \to l+1)\right]\right\rangle$$

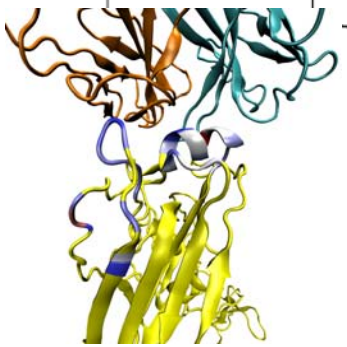
  - Inference from bioinformatics analysis of viral abundance data (FluNet, WHO database, IEDB, UCLA-Layne)
- Free energy calculations consistent with animal model testing and retrospective 1970s human sequence data

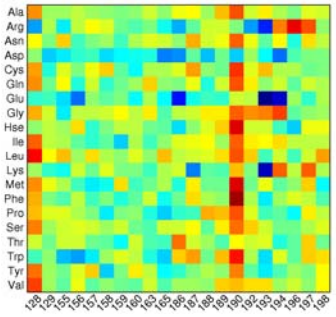


Calculate Flu Free Energy Changes Due to aa Substitution

- Statistical Mechanics $\frac{K_1}{K_0} = \exp(-\Delta\Delta G/RT)$
- Details associated with thermodynamic integration
- Hess's Law: ΔΔG=ΔG42 - ΔG31 = ΔG43 - ΔG21





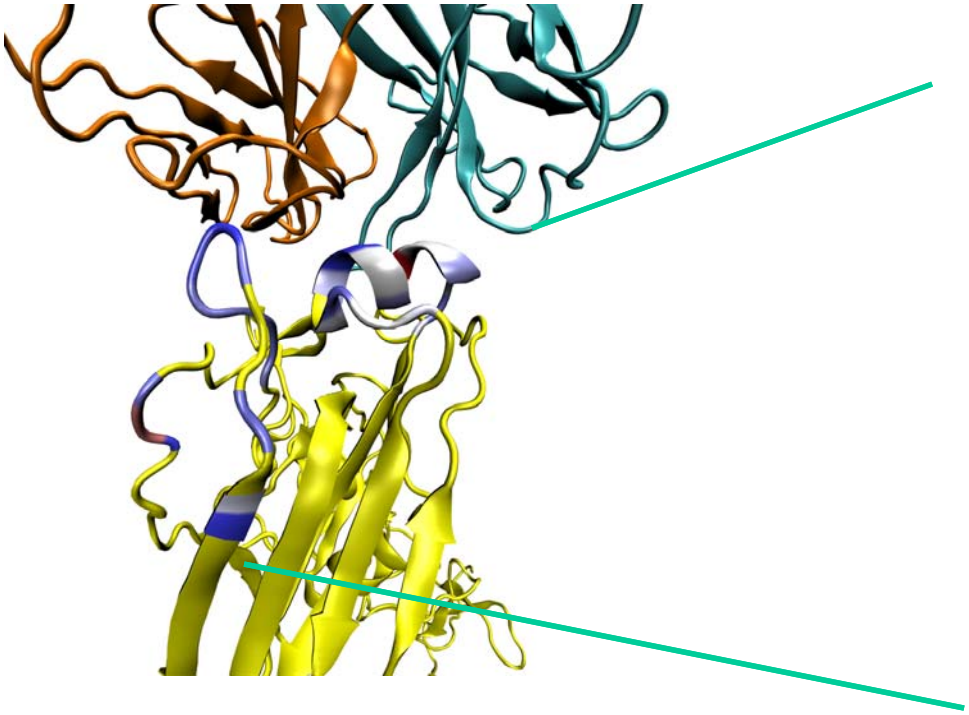


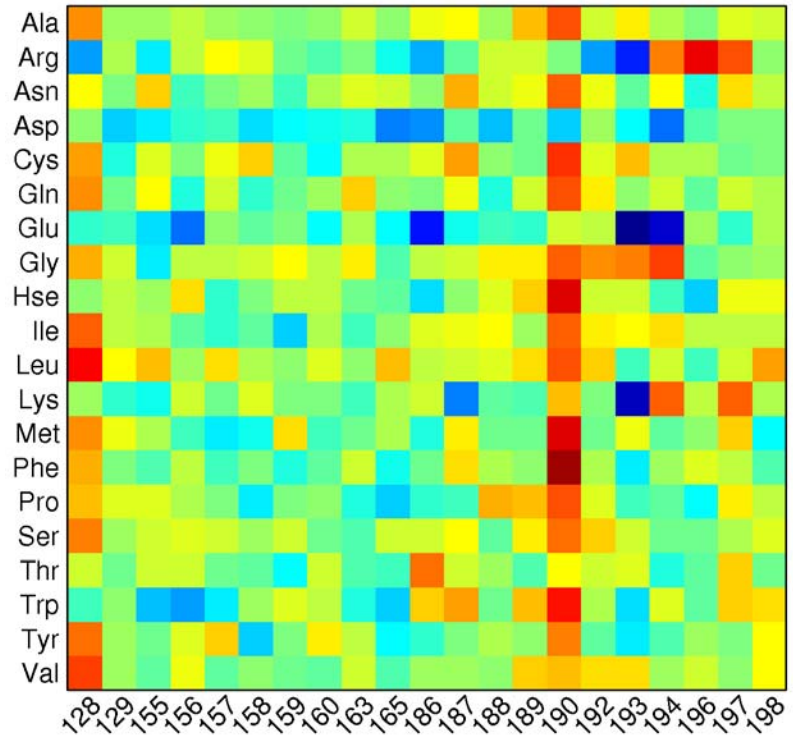
Pan and Deem, *J. Chem. Theory Comput.* **7** (2011) 1259

- Detailed molecular calculation of virus fitness
- Simple interpretation: charge is disruptive, allowing virus to escape immune system

ΔΔG Values

positions	128	129	155	156	157	158	159
Ala	−13.12 ± 0.27	3.33 ± 0.29	2.78 ± 0.20	1.19 ± 0.33	2.48 ± 0.21	4.27 ± 0.31	5.18 ± 0.21
Arg	22.57 ± 0.46	2.31 ± 0.45	16.98 ± 0.37	0.08 ± 0.50	−4.19 ± 0.44	−1.61 ± 0.48	7.07 ± 0.42
Asn	−4.80 ± 0.36	5.83 ± 0.42	−7.83 ± 0.30	10.72 ± 0.40	5.64 ± 0.34	3.41 ± 0.42	10.97 ± 0.35
Asp	4.52 ± 0.38	19.12 ± 0.42	16.28 ± 0.32	11.06 ± 0.42	9.95 ± 0.37	18.37 ± 0.40	15.34 ± 0.36
Cys	−11.83 ± 0.34	12.64 ± 0.37	−2.37 ± 0.30	5.32 ± 0.38	−2.72 ± 0.29	−7.88 ± 0.40	7.92 ± 0.32





Average ΔΔG Values

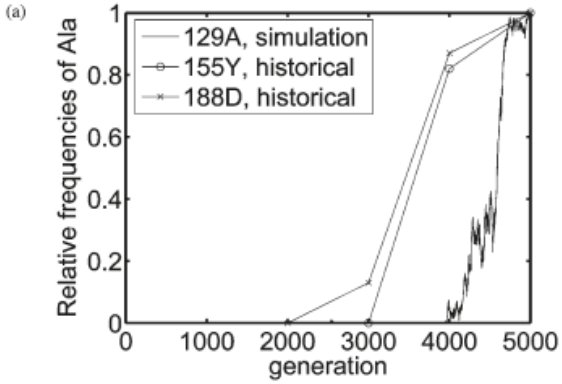
- Charge is disruptive

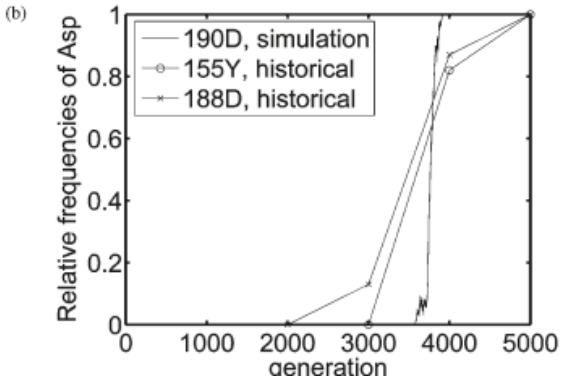
Table 2. Rank of the Average Binding Free Energy Difference of the Single Substitution from Alanine to Another Amino Acid over All 21 Amino Acid Sites in Epitope B of Hemagglutinin Trimer[a]

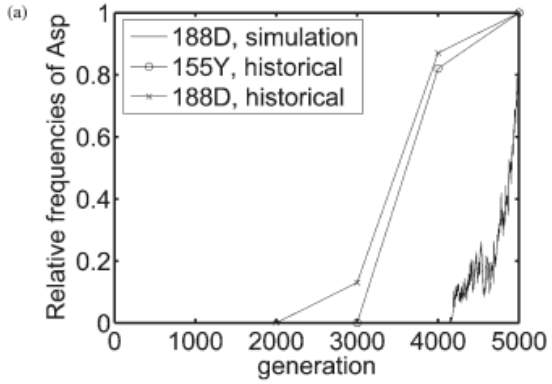
rank	amino acid	ΔΔG(kcal/mol)	charged	hydrophobic	large	medium	small	relative frequency
1	Glu	14.612 ± 0.061	×		×			0.029
2	Asp	14.533 ± 0.055	×			×		0.051
3	Arg	6.018 ± 0.078	×		×			0.052
4	Lys	5.766 ± 0.078	×		×			0.057
5	Trp	4.458 ± 0.081		×	×			0.016
6	Tyr	3.984 ± 0.071		×	×			0.035
7	Thr	3.981 ± 0.050				×		0.078
8	Pro	3.912 ± 0.054		×		×		0.060
9	Met	3.562 ± 0.062		×	×			0.009
10	Phe	3.522 ± 0.073		×	×			0.030
11	Hse	2.654 ± 0.064			×			0.020
12	Gln	1.985 ± 0.063			×			0.042
13	Ile	1.396 ± 0.060		×	×			0.070
14	Asn	1.150 ± 0.054				×		0.085
15	Val	1.147 ± 0.051		×		×		0.055
16	Cys	0.888 ± 0.046				×		0.028
17	Ser	0.469 ± 0.044					×	0.096
(18)	(Ala)	(0.000 ± 0.000)		×			×	0.046
19	Gly	−1.612 ± 0.055		×			×	0.070
20	Leu	−2.273 ± 0.064		×	×			0.071

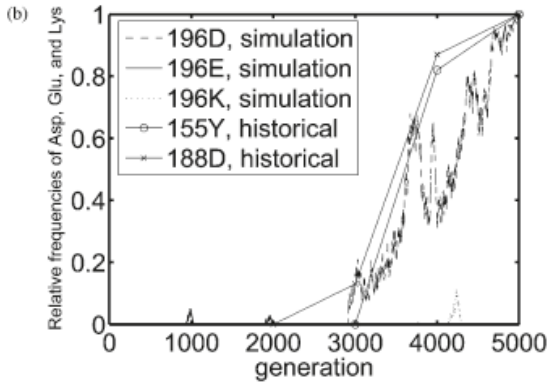
Modeling Viral Dynamics

- Viral dynamics for some early substitutions in humans 1970-1973
- Mutation rate from observation
- Fitness proportional to ΔΔG



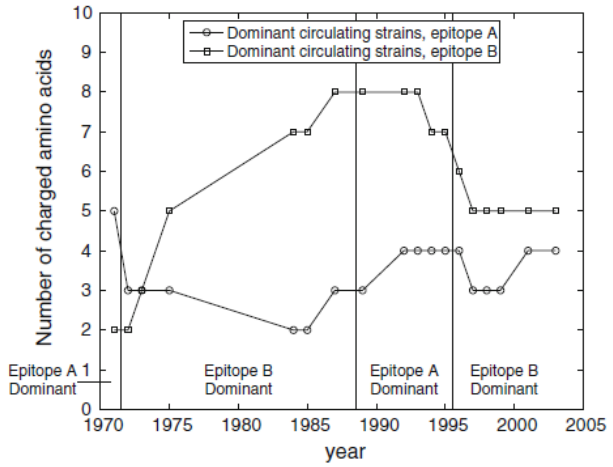


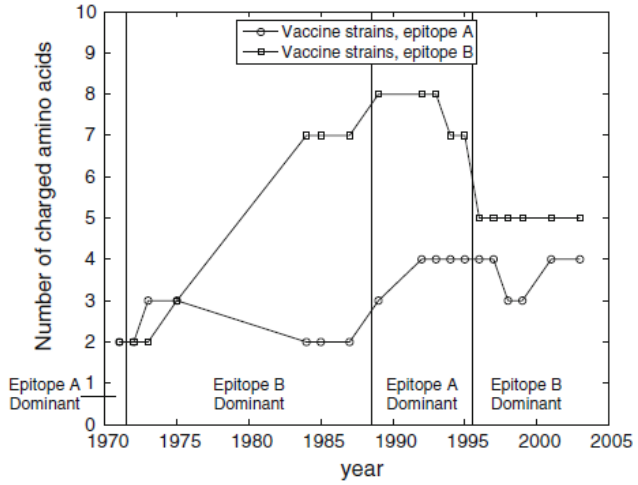




The Hong Kong flu in Humans

- E.g. virus may increase charge in epitope region
- Track fraction of Asp, Glu, Arg, Lys, His
- Charge does increase in dominant epitope, early on





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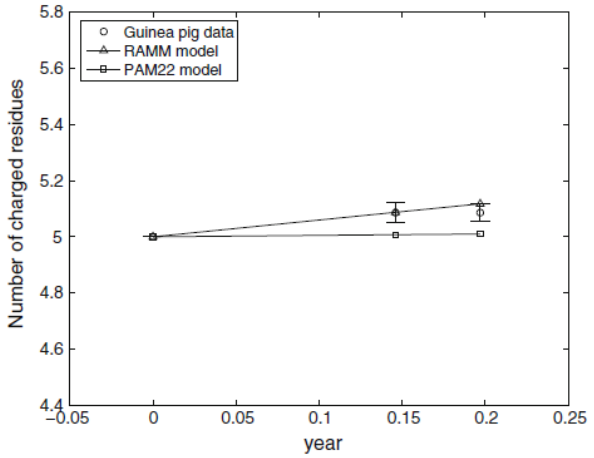
Substitutions 1968-1975

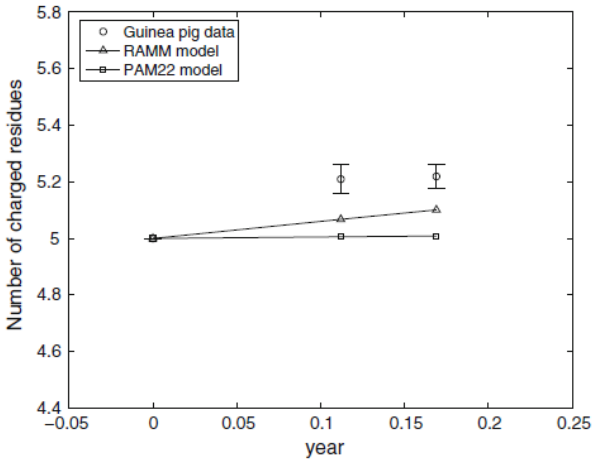
Table 4. Substitutions Occurred in Epitope B of the Hemagglutinin A/Aichi/2/1968 (H3N2) as of 1975[a]

substitution	year	ΔΔG (kcal/mol)	rank (substituting)	rank (WT)
T128N	1971	−4.796 ± 0.361	8	7
T128I	1975	−16.026 ± 0.412	18	7
G129E	1970, 1972	10.500 ± 0.415	4	17
T155Y	1972−1973, fixed in 1973	7.254 ± 0.358	9	14
G158E	1971−1972	8.584 ± 0.479	6	17
S159N	1971, 1974−1975	10.969 ± 0.352	5	17
S159C	1972	7.923 ± 0.324	6	17
S159R	1972	7.065 ± 0.424	7	17
T160A	1973	4.160 ± 0.217	11	18
S186N	1975	4.673 ± 0.298	10	14
N188D	1971−1973, fixed in 1973	19.767 ± 0.367	1	14
Q189K	1975	9.484 ± 0.640	2	10
E190 V	1972	−9.115 ± 0.310	5	3
E190D	1975	18.752 ± 0.324	1	3
S193N	1972−1975	8.239 ± 0.301	10	12
S193D	1975	15.285 ± 0.294	7	12
A198T	1972	6.793 ± 0.236	3	14

Animal Models also Show Selection Pressure

- Guinea pigs infected with
  - CDC A/Wyoming/2003 virus mixture
  - Homogeneous WyB4 virus isolate
- Naïve, primary, secondary responses



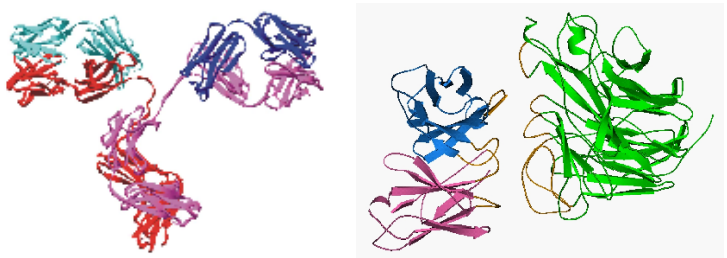


J. Mol. Evol. (2011) **72**:90–103

Model of Antibody Structure and Function

S. Kauffman and S. Levin, *J. Theor. Biol.* **128** (1987) 11
S. A. Kauffman and W. G. MacCready, *J. Theor. Biol.* **173** (1995) 427
A. S. Perelson and C. A. Macken, *Proc. Natl. Acad. Sci. USA* **92** (1995) 9657
L. D. Bogarad and M. W. Deem, *Proc. Natl. Acad. Sci. USA* **96** (1999) 2591

A generalized NK model



- M = 10 subdomains
- N = 10 amino acids per subdomain
- L = 5 different subdomain types (helices, strands, loops, turns, others)
- Q = 5 classes of amino acids (negative, positive, polar, hydrophobic, other)

$$U = \sum_{i=1}^{M} U_{\alpha_i}^{\mathrm{sd}} + \sum_{i>j=1}^{M} U_{ij}^{\mathrm{sd-sd}} + \sum_{i=1}^{P} U_i^{\mathrm{c}}$$

Gaussian σ

$$U_{\alpha_i}^{\mathrm{sd}} = \frac{1}{[M(N-K+1)]^{1/2}} \sum_{j=1}^{N-K+1} \sigma_{\alpha_i}\left(a_j, a_{j+1}, \ldots, a_{j+K-1}\right) \qquad K = 4$$

$$U_{ij}^{\mathrm{sd-sd}} = \left[\frac{2}{DM(M-1)}\right]^{1/2} \sum_{k=1}^{D} \sigma_{ij}^{(k)}\left(a_{j_1}^{(i)}, \ldots, a_{j_{K/2}}^{(i)}; a_{j_{K/2+1}}^{(j)}, \ldots a_{j_K}^{(j)}\right) \qquad D = 6$$

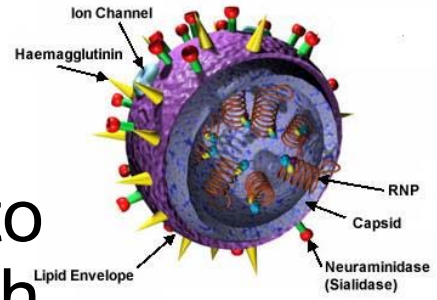
$$U_i^{\mathrm{c}} = \frac{1}{\sqrt{P}} \sigma_i\left(a_i\right) \qquad P = 5$$

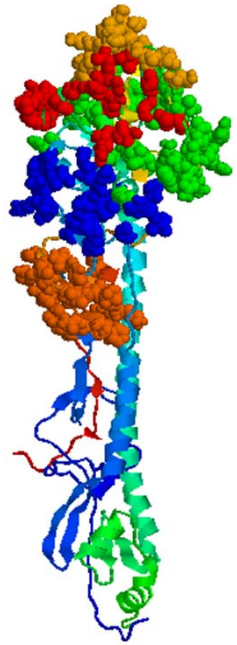
Energy → Binding constant

Parameters → Antigen

The Order Parameter $p_{epitope}$

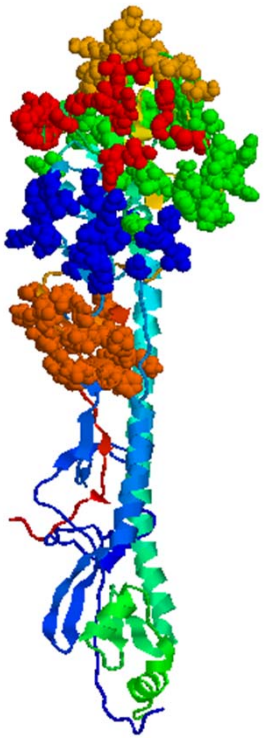
- The theory is a form of spin glass model, first used to describe nuclear cross sections, e^- spins in solid
- Mutation of the flu virus corresponds to changing parameters in the model with probability p
- In the immune system, $p_{epitope}$ is the fraction of amino acids that change in the dominant epitope
- We observe the effectiveness of vaccination to subsequent exposure to the flu

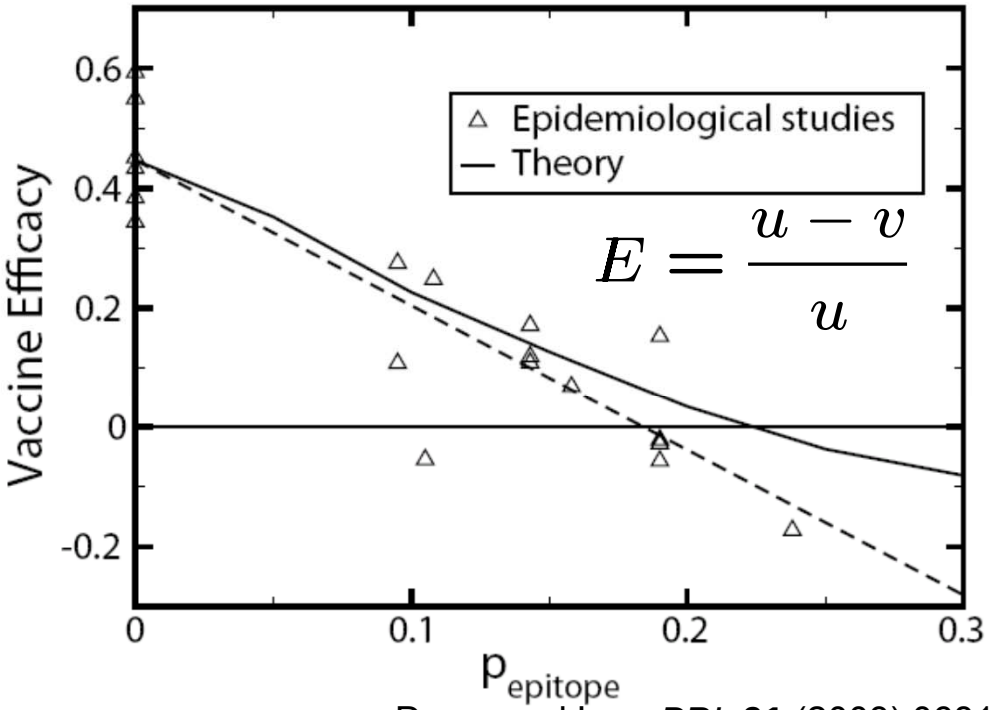


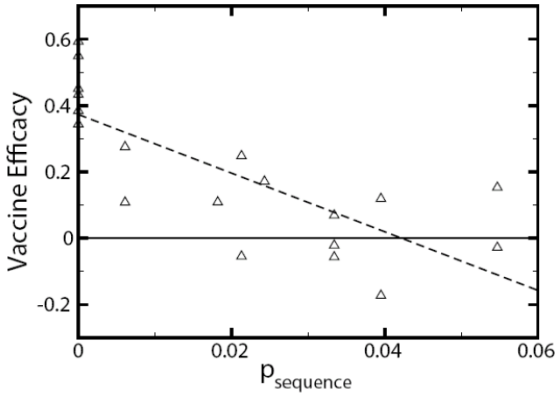


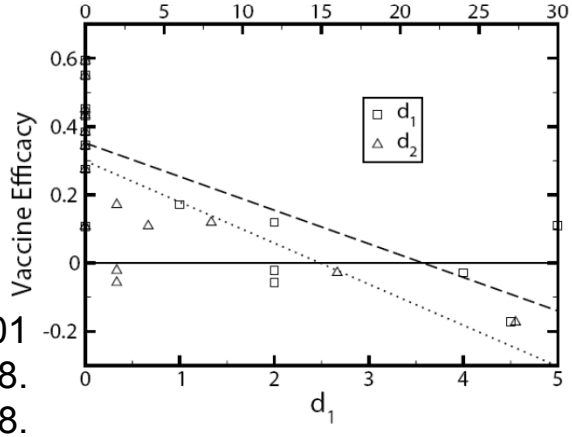
Vaccine Effectiveness

- H3N2 human effectiveness from last 35 years (epidemiological)
- Effectiveness correlates well with $p_{epitope}$
- $p_{sequence}$ & d_{ferret} correlate modestly with human effectiveness
- Negative effectiveness is mostly at large $p_{epitope}$ (OAS)
- Theory validates correlation







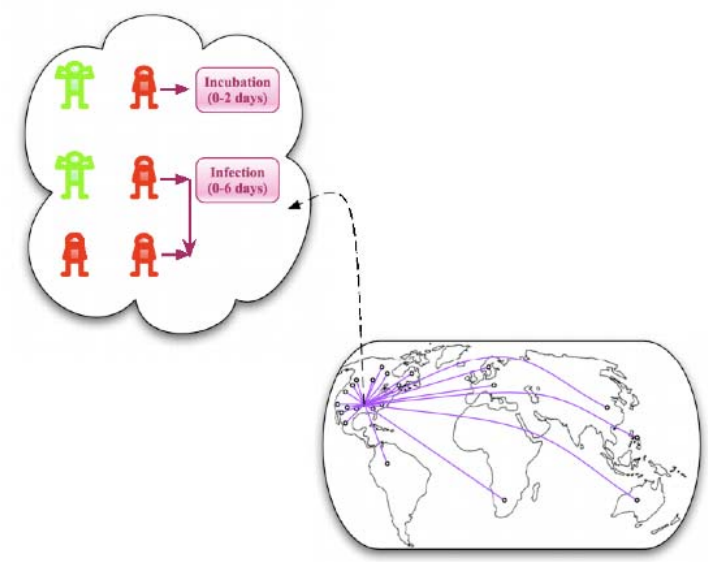


Deem and Lee, *PRL* **91** (2003) 068101
Gupta, Earl, and Deem, *Vaccine* **24** (2006) 3881-3888.
Munoz and Deem, *Vaccine* **23** (2005) 1144-1148.

H. Zhou, R. Pophale, and M. W. Deem, ``Computer-Assisted Vaccine Design,'' in *Influenza: Molecular Virology*, Horizon Scientific Press (2009)

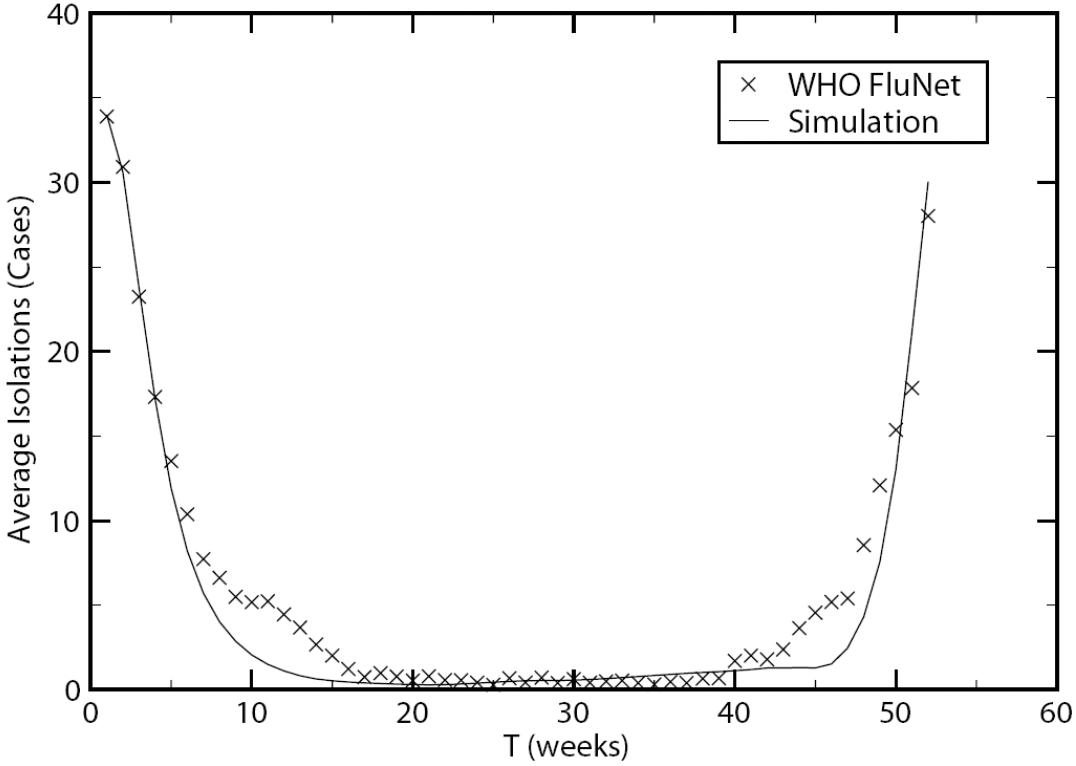
Stochastic Model of Influenza Spread and Evolution

- Global Hierarchical Scale Free Network
  - Human distribution
  - Worldwide air transportation
  - Person to person contact within city
- Virus Transmission & Evolution
  - Contact based transmission
  - Evolution derived by mutation



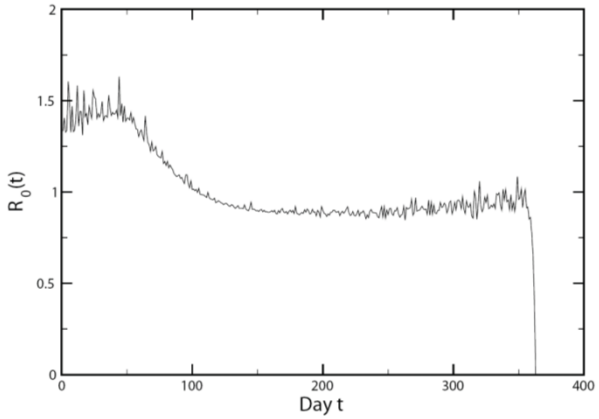
Model Prediction

- Simulation & FluNet Data Comparison



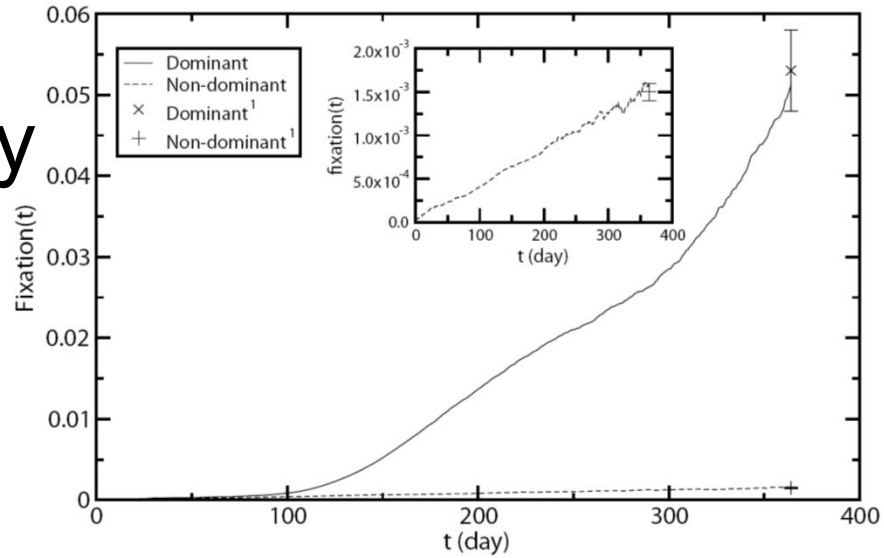
Reproductive Ratio

- R_0 should be a prediction of the model, not an input
- R_0 is time dependent
- R_0 is spatially dependent



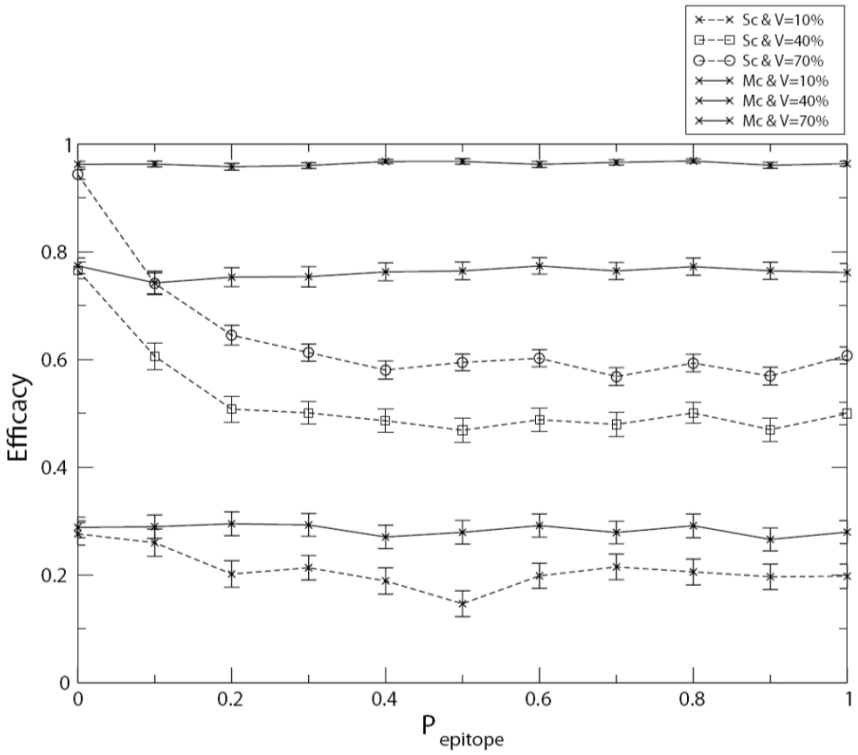
Viral Diversity

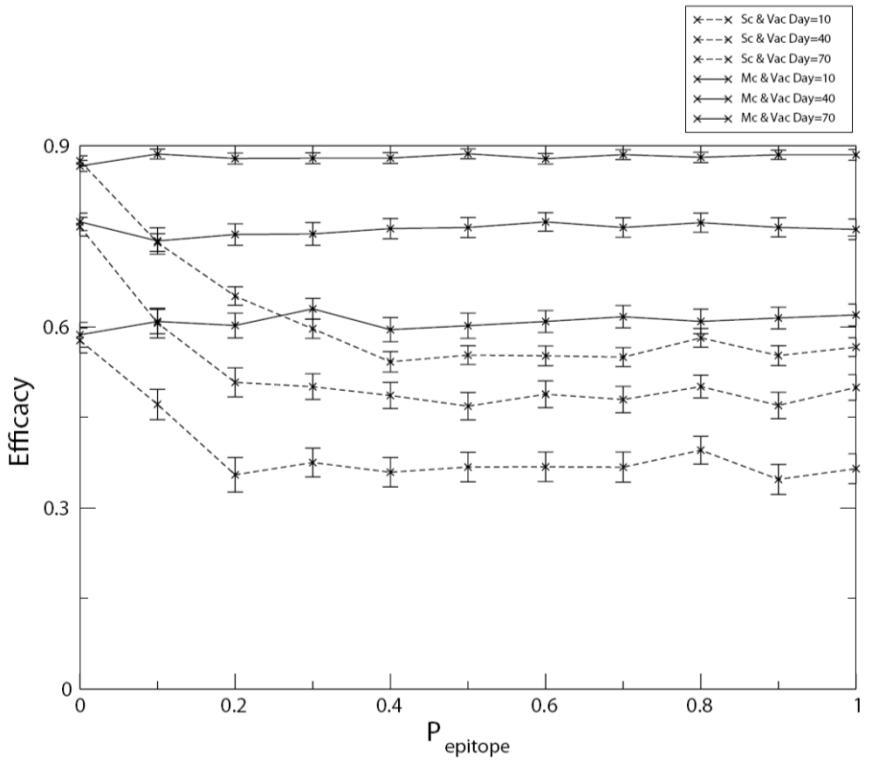
- Quantify viral diversity and expected vaccine effectiveness
- Expect more diversity late in the season
- Because pressure to evolve exists only as virus is being eradicated



Mitigation Strategies for Flu Pandemics

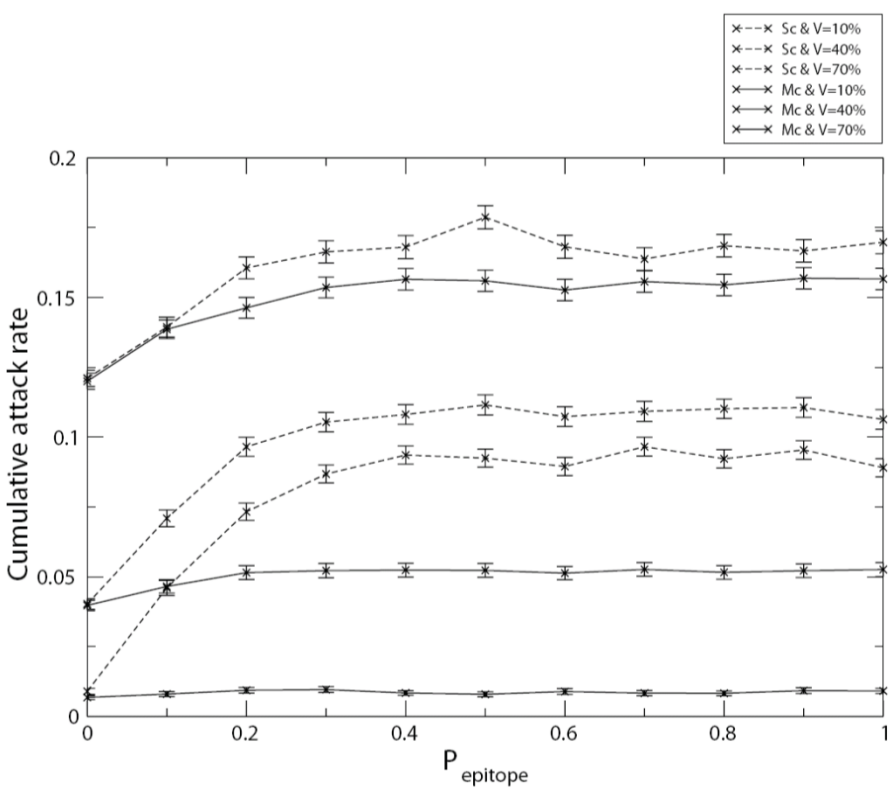
- Quantify expected vaccine effectiveness, 2 initial strains
- Different percentages of population vaccinated
- Vaccination at different days
- Single-component or multi-component vaccine

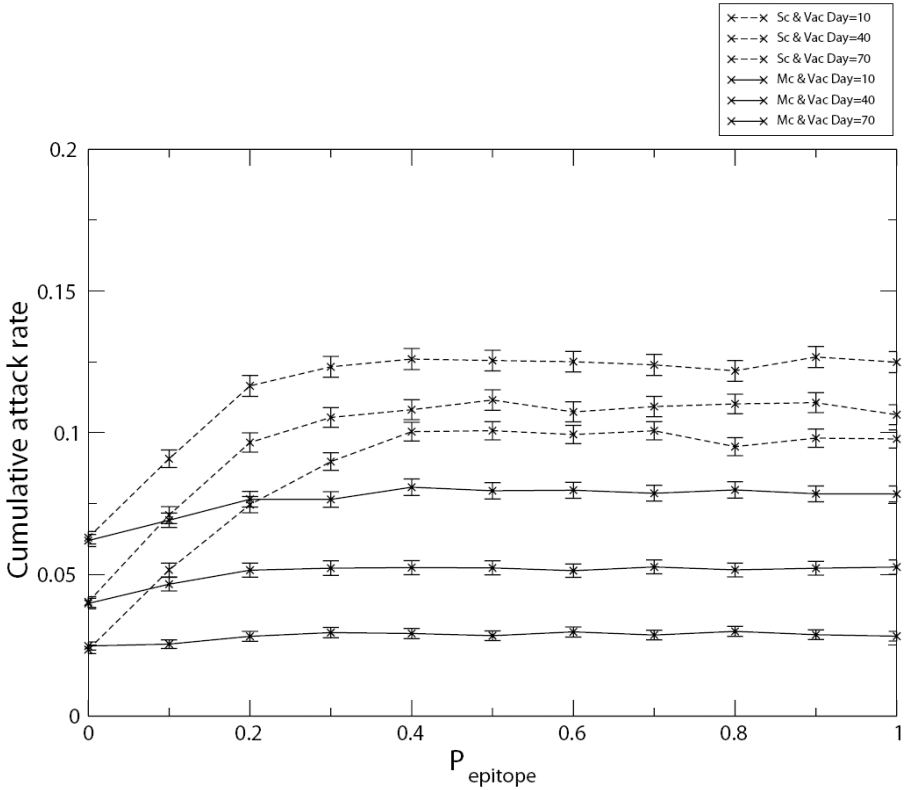




Mitigation: Attack Rate

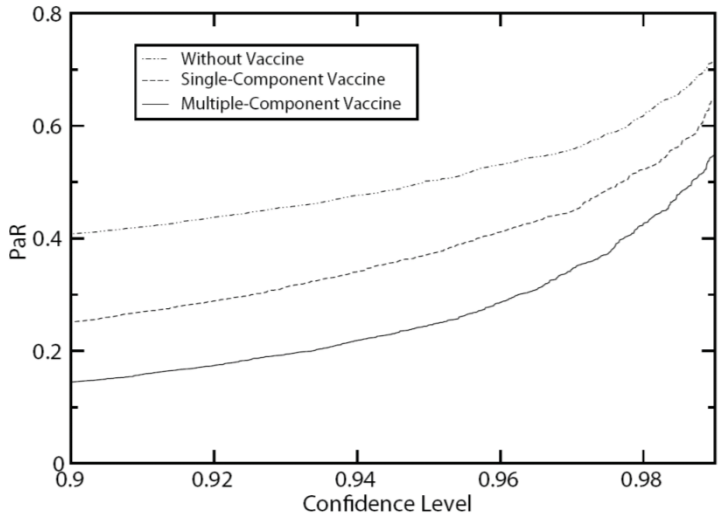
- As vaccine effectiveness goes down the attack rate goes up





Risk Analysis: Population at Risk (PaR)

- PaR: The fraction of the population that will be infected in a X% of worst-case epidemic
- Depends on vaccination strategy

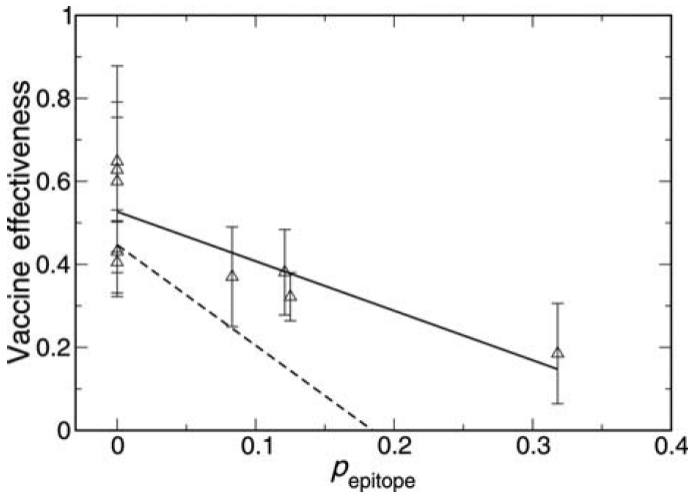


H1N1 Epidemic Progression

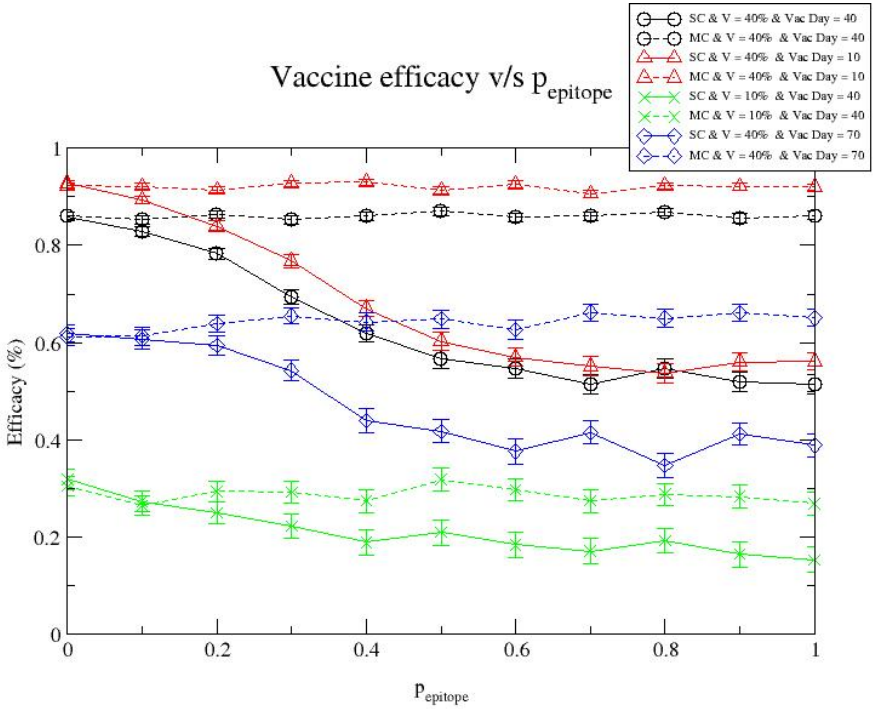
- Agent-based model
- 6.7B people, North and South hemisphere
- Transmission between people, long-distance and local
- Virus evolution within people, with immune pressure
- Single or multiple strain seeding of epidemic
- Vaccination at different delays and of different fractions of population

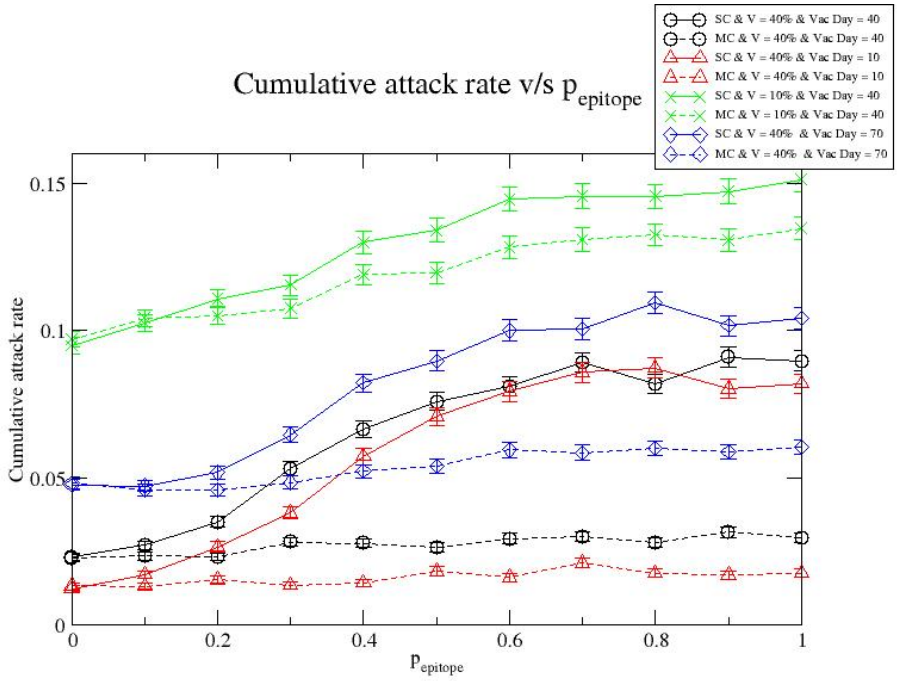
After: Zhou, H., Pophale, R. S., and Deem, M. W. (2009). Computer-Assisted Vaccine Design, in Influenza: Molecular Virology, Horizon Scientific Press, edited by Qinghua Wang and Yizhi Jane Tao, pp. 173-191.

H1N1 Vaccine effectiveness in an Epidemic



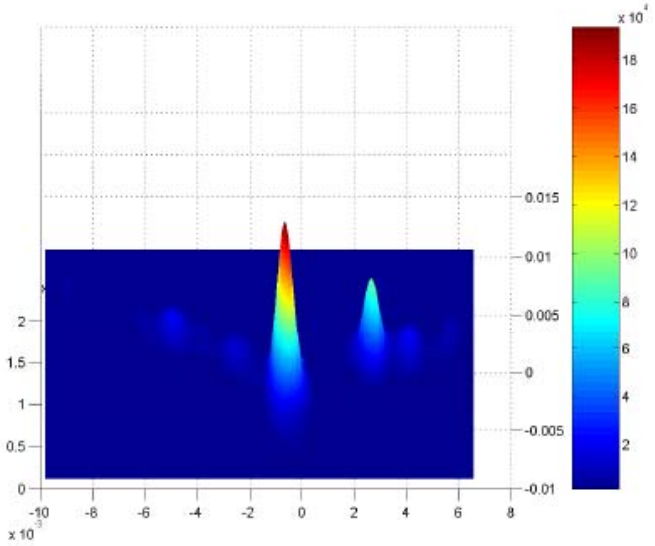
- Effectiveness: ε = (u-v)/u
- Attack rate: fraction of population infected



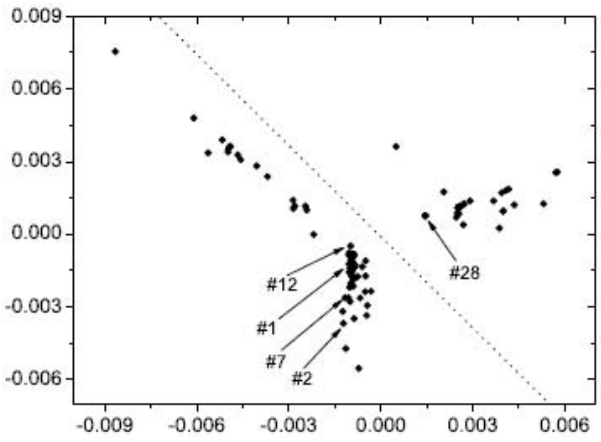


Clustering to Detect Strains

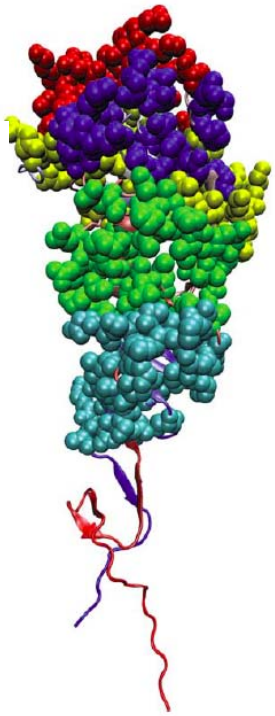
- Standard dimensional scaling
- Project sequence to best 2 dimensions
- Kernel density estimation



(a)



(b)

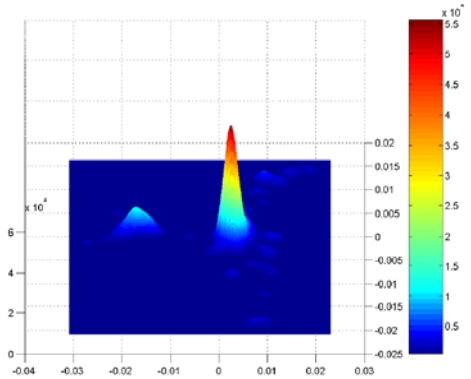


#12: A/Texas/05/2009

#28: A/New York/19/2009

Criteria for New Strains

- Criteria
  - New strain is in cluster found by kernel density estimation
  - $p_{epitope}$ between new cluster and current dominant strain cluster is larger than size of new cluster
  - Analysis performed in most informative 2-D subspace
- Is sequence enough?
- Are there enough data?

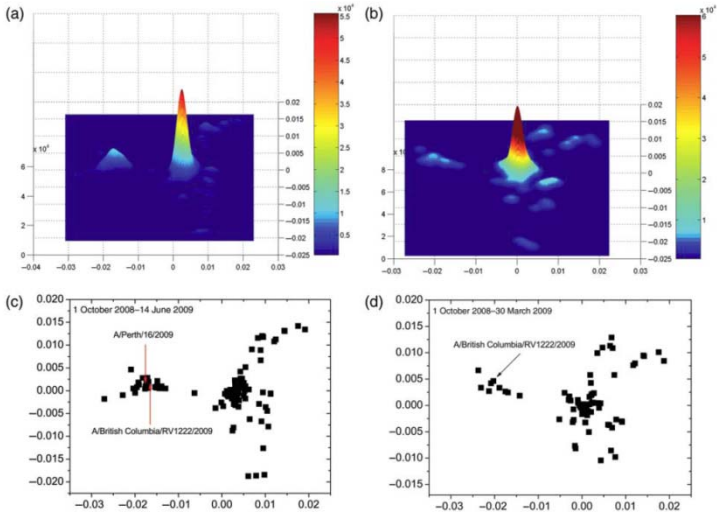


Detection of New Influenza Strains

Protein Engineering, Design & Selection 23 (2010) 935

- New modules are detectible with statistical techniques
- There are enough data to see new clusters
- E.g. novel H3N2 strain in 2009 detected 15 days after first sequencing

Sequence, not ferret, data



J. He and M. W. Deem *PEDS* **23** (2010) 935

Cluster Transitions

- Virus stays within quasispecies for 3-5 years
- Then makes transition to new cluster
- We detect the emergence of the new cluster 1-2 years before it fixes in human population

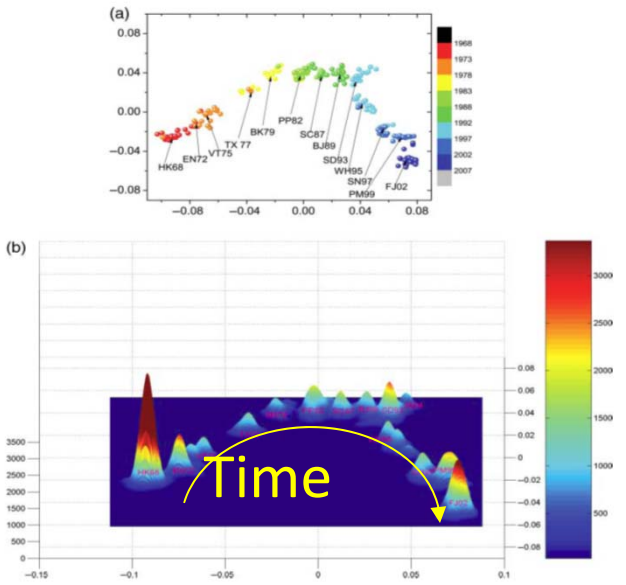


Table I. Summary of results

Flu season	Vaccine strain from WHO (World Health Organization, 2009c)	Our prediction	Circulating H3N2 strain	Circulating subtype
1996–1997	Wuhan/359/95	Wuhan/359/95	Wuhan/359/95	H3
1997–1998	Wuhan/359/95	Wuhan/359/95	Sydney/5/97	H3
1998–1999	Sydney/5/97	Sydney/5/97	Sydney/5/97	H3
1999–2000	Sydney/5/97	Sydney/5/97	Sydney/5/97	H3
2000–2001	Panama/2007/1999	Panama/2007/1999	N/A	H1
2001–2002	Panama/2007/1999	Panama/2007/1999	Panama/2007/1999	H3
2002–2003	Panama/2007/1999	Fujian/411/2002	N/A	H1
2003–2004	Panama/2007/1999	Fujian/411/2002	Fujian/411/2002	H3
2004–2005	Fujian/411/2002	Fujian/411/2002	Fujian/411/2002	H3
2005–2006	California/7/2004	California/7/2004	California/7/2004	H3
2006–2007	Wisconsin/67/2005	Wisconsin/67/2005	Wisconsin/67/2005	H3
2007–2008	Wisconsin/67/2005	Wisconsin/67/2005	N/A	H1
2008–2009	Brisbane/10/2007	Brisbane/10/2007	Brisbane/10/2007	H3
2009–2010	Brisbane/10/2007	BritishColumbia/RV1222/09	BritishColumbia/RV1222/09	H1
2010–2011	Perth/16/2009	BritishColumbia/RV1222/09	N/A	N/A

Conclusions

- Spin glass theory (GNK model) of immune response
- Multisite vaccination for dengue fever, HIV, cancer
- Vaccine effectiveness for influenza, and influenza evolution
- Evolution of influenza due to pressure from prior history of infection or vaccine