

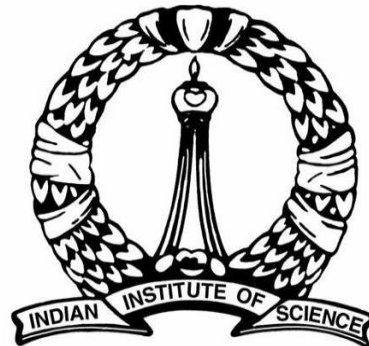
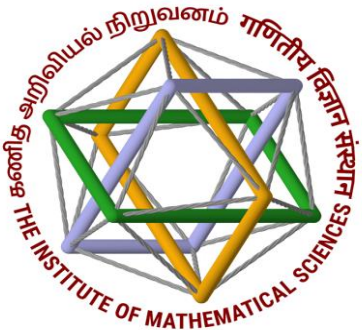
Incorporating genetic heterogeneity into epidemic models for H1N1 influenza

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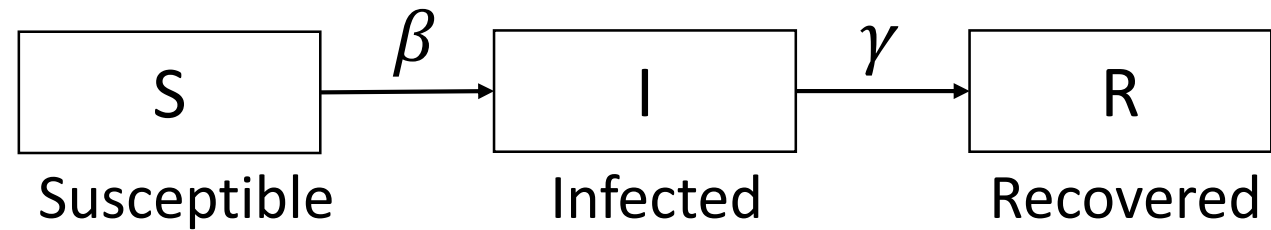
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SIR model predicts final epidemic size

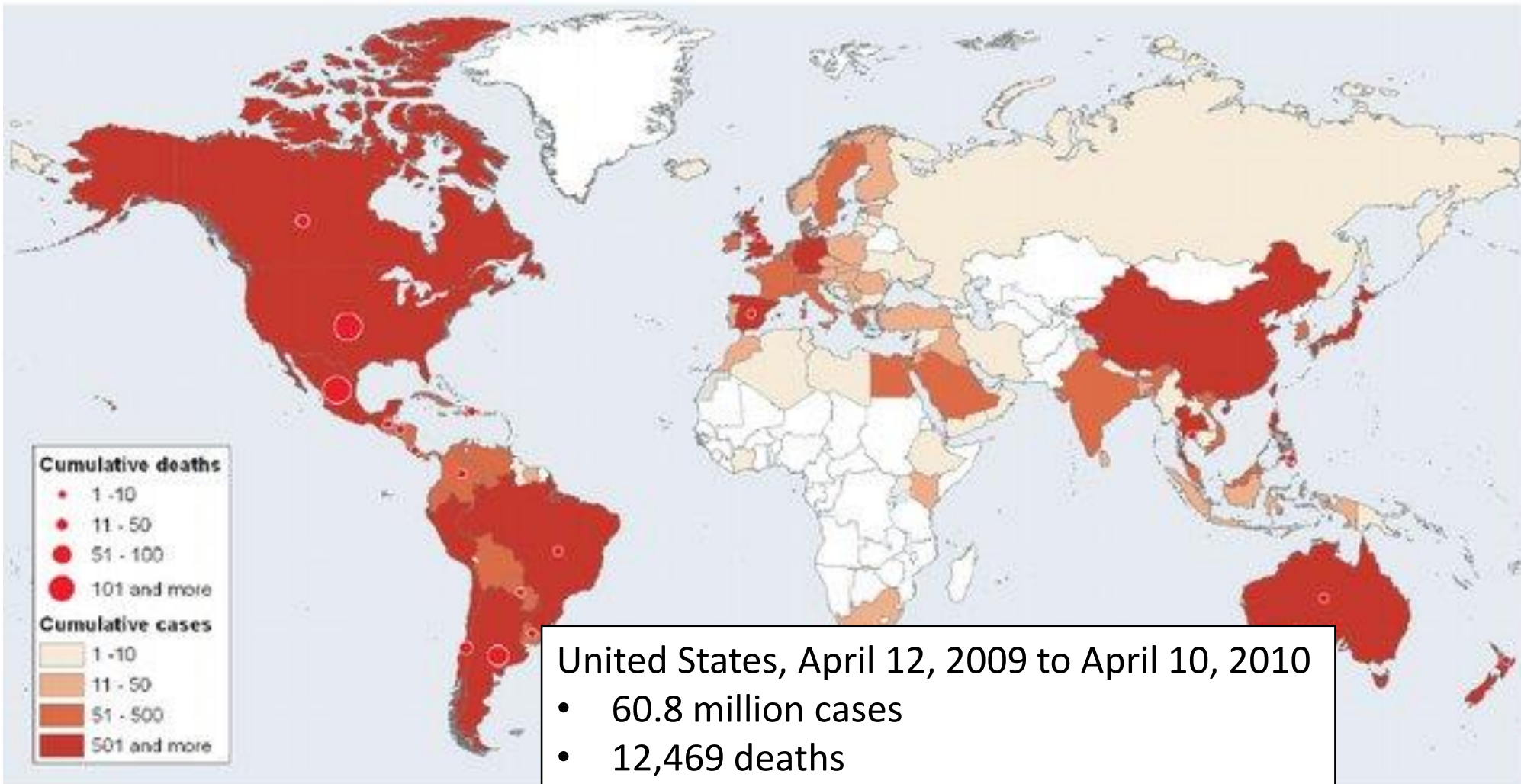


- Assumption - Homogeneous susceptibility, infectivity and recovery

Heterogeneity exists: H1N1 swine flu pandemic

Pandemic (H1N1) 2009,
Number of laboratory confirmed cases as reported to WHO

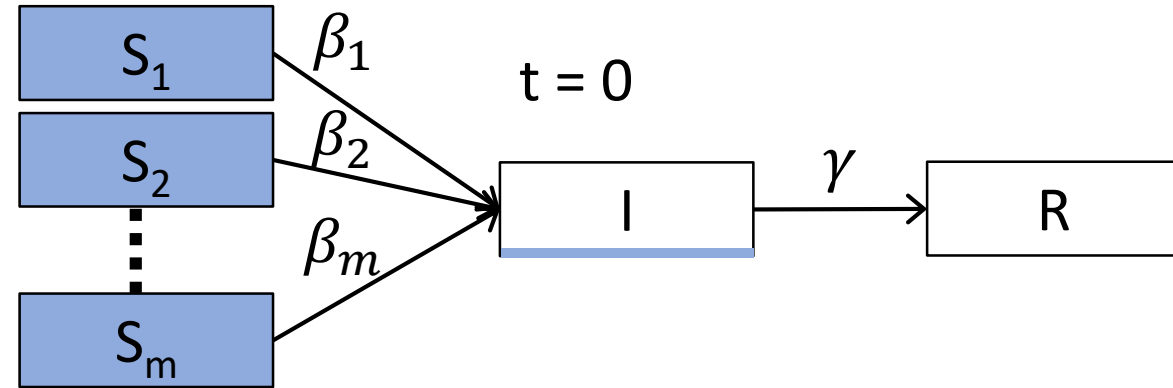
Status as of 06 July 2009
09:00 GMT



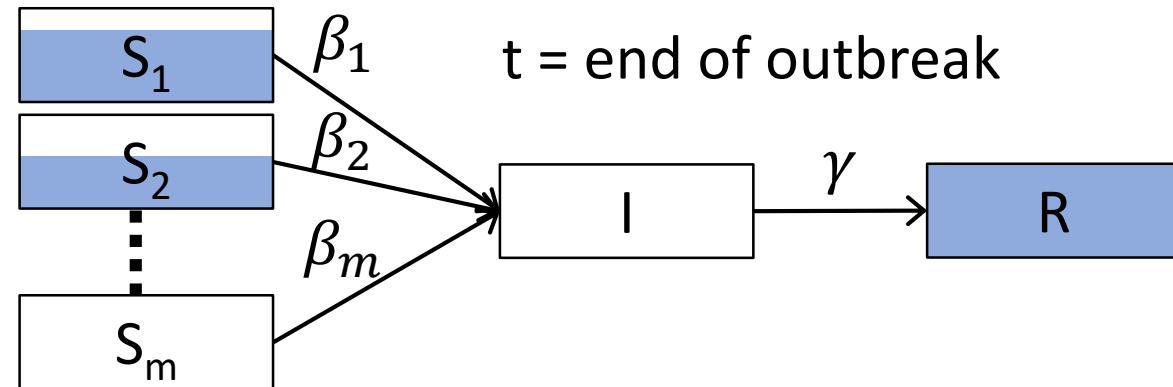
United States numbers reported by CDC: https://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm

Genetic heterogeneity in host and pathogen

- Susceptibility sub-groups
 - Equal susceptibility within a sub-group
 - Different susceptibility across sub-groups
 - Recovery rate remains constant



- To be estimated
 - Number of susceptibility sub-groups
 - Size of each sub-group
 - Beta for each sub-group



Our contribution: Host - Pathogen Immune Interaction

Immune response to viral infection - CD8+ T cell

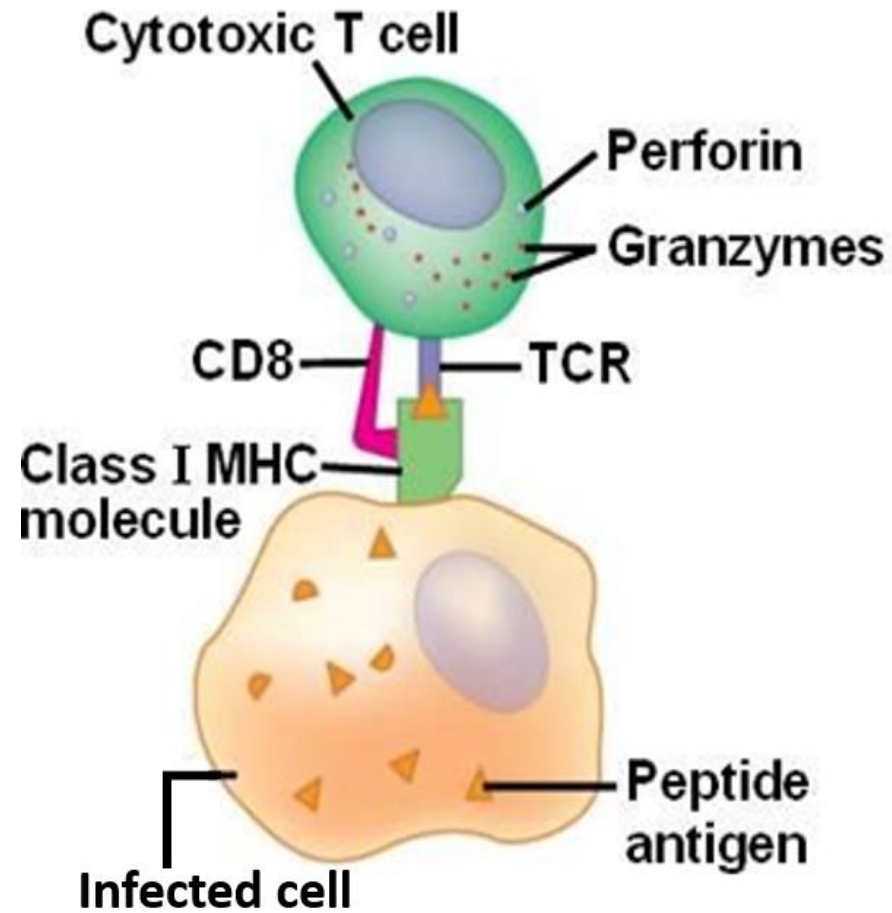


Image courtesy: Campbell, Neil A., et al. "Biology, eighth edition." *San Francisco* (2008).

Immune response to viral infection - CD8+ T cell

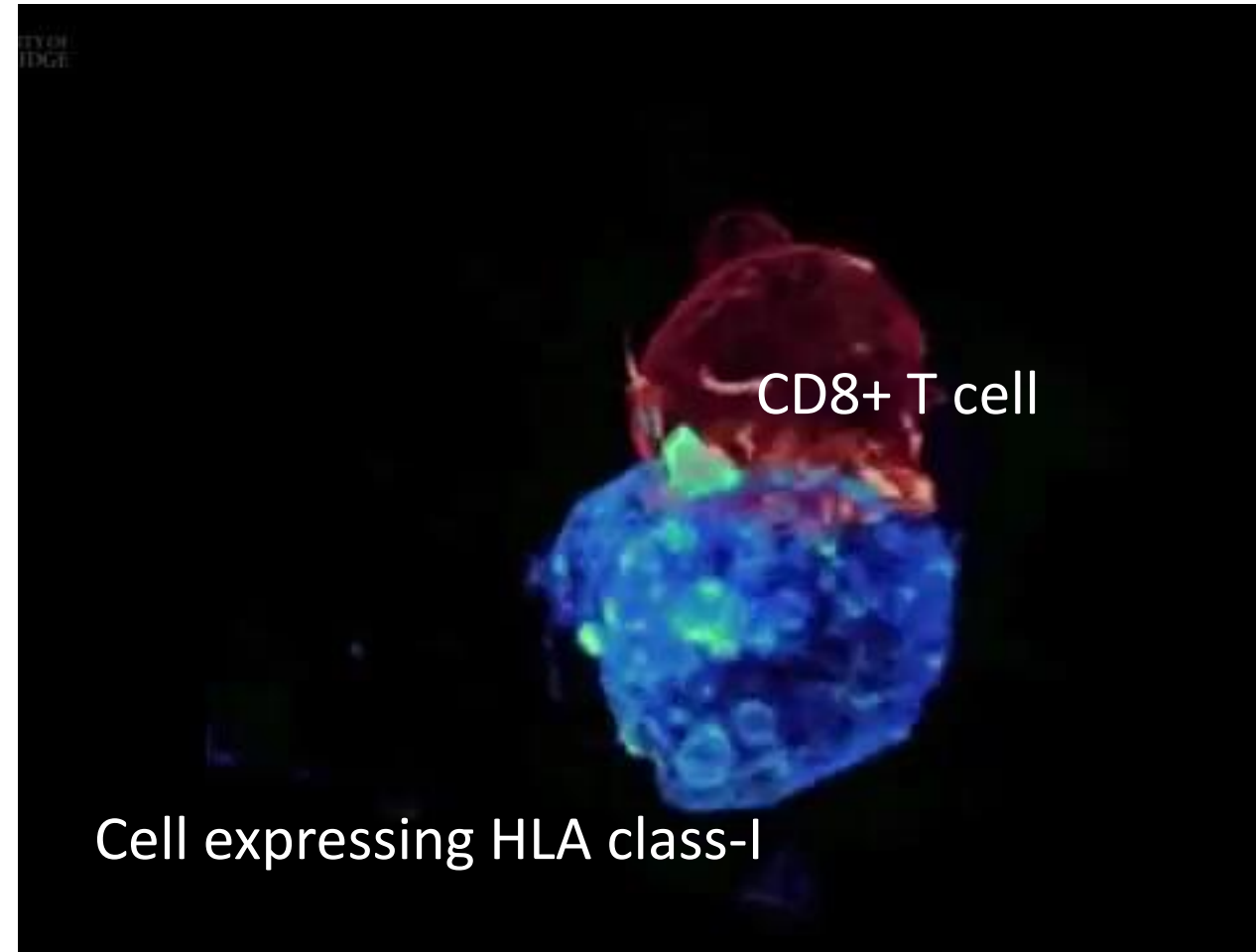
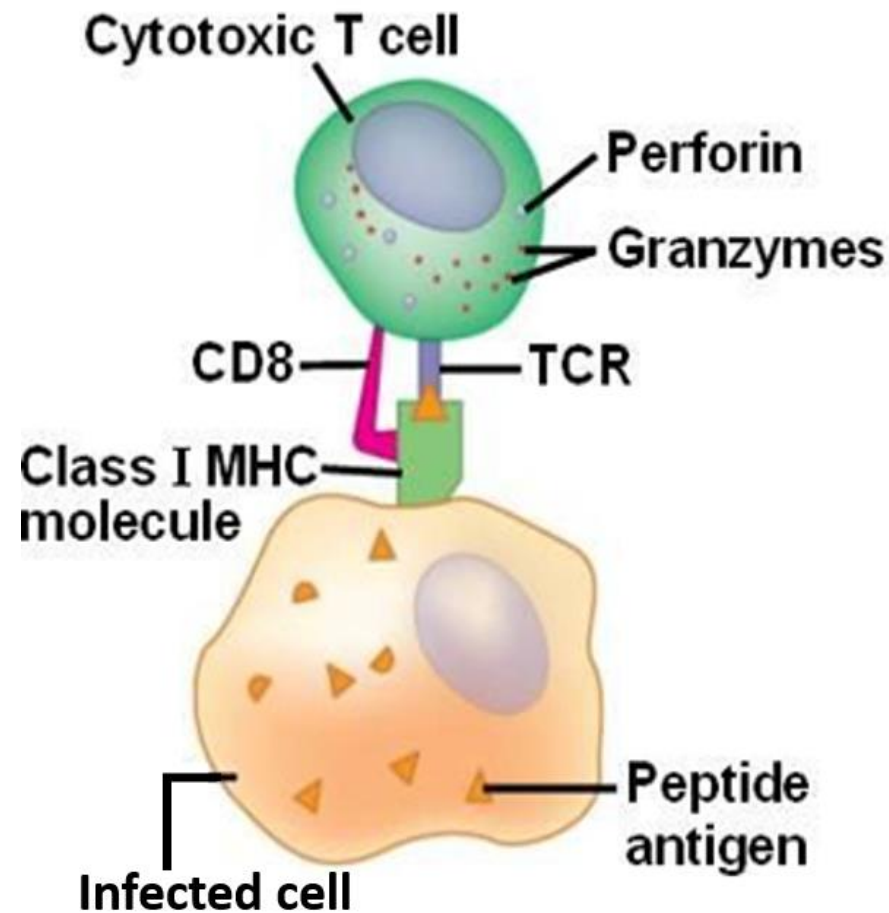
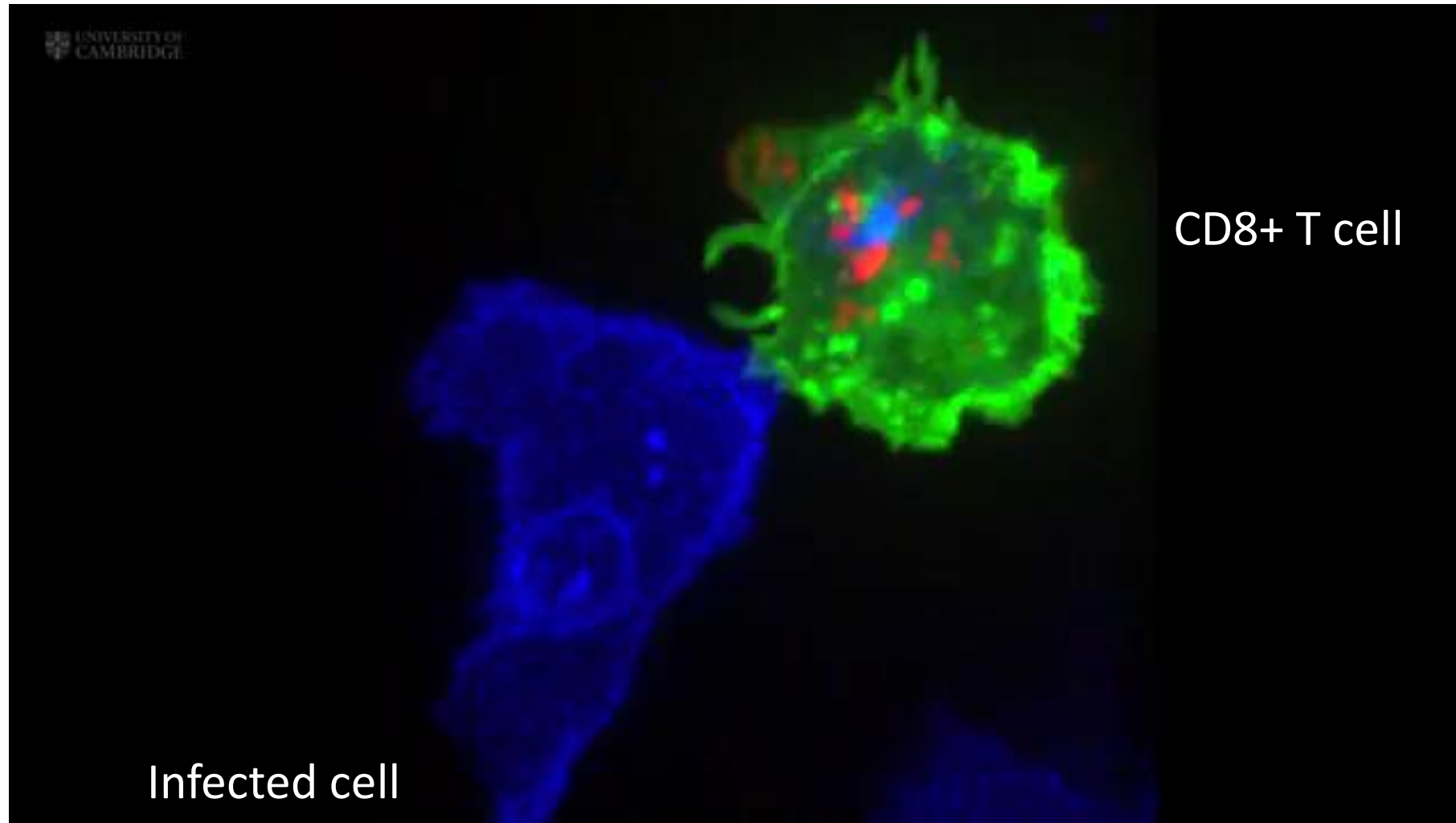


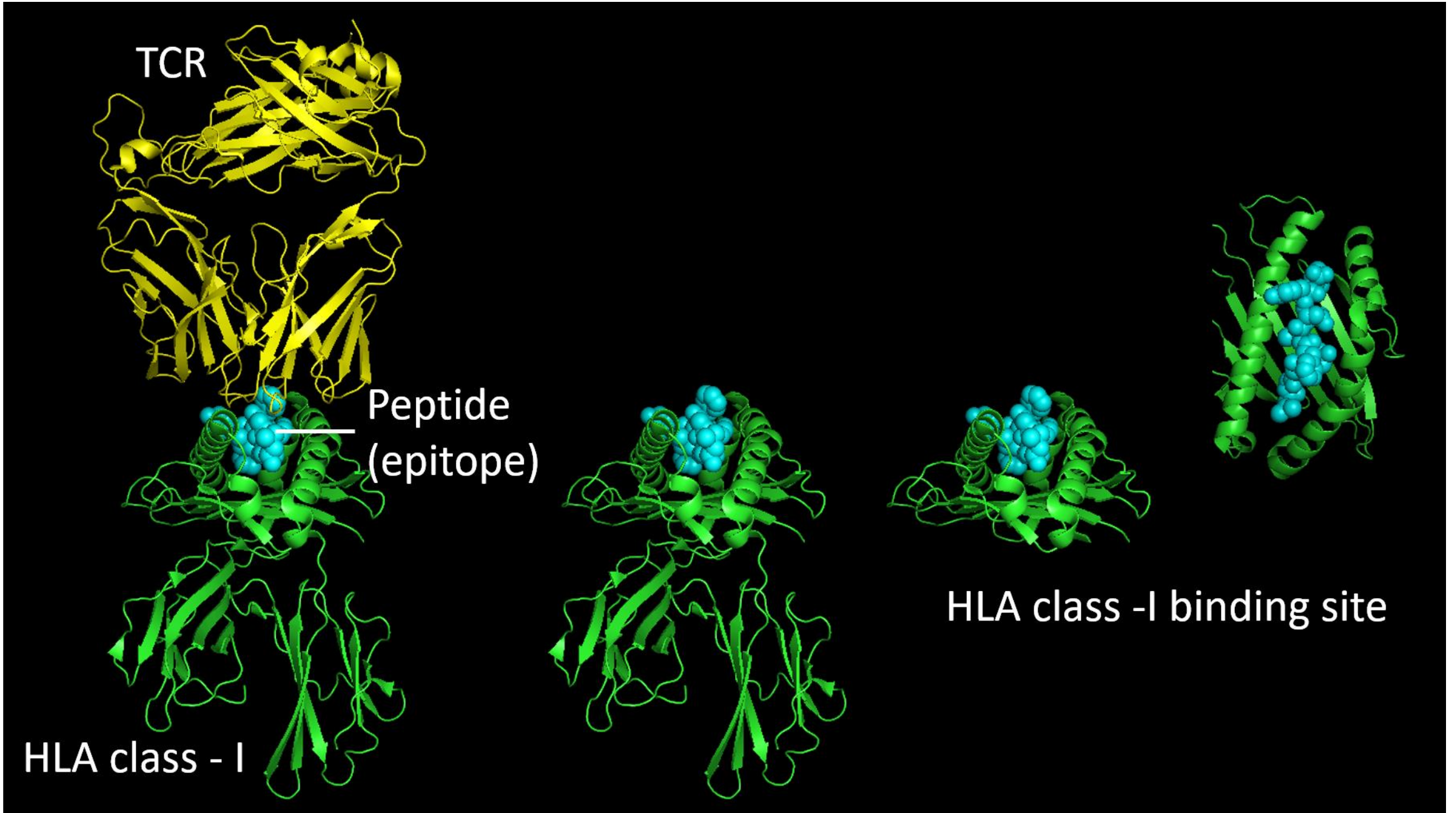
Image courtesy: Campbell, Neil A., et al. "Biology, eighth edition." *San Francisco* (2008).

Video courtesy: "Killer T Cell: The Cancer Assassin" Cambridge University, May2015. <https://www.youtube.com/watch?v=ntk8XsxVDi0>

CD8+ T cell attacking an infected cell



Molecules involved in the binding



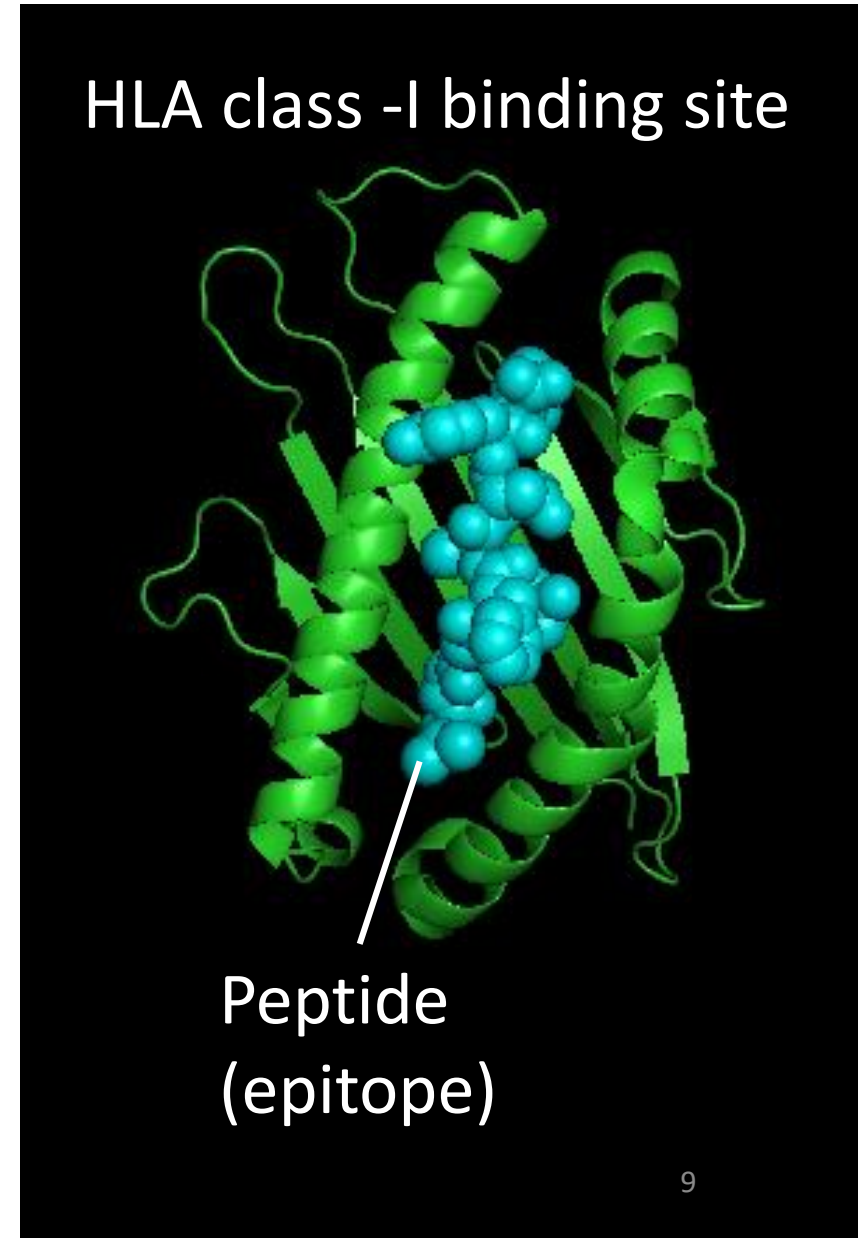
Conditions for CD8+ T cell response

1. **Peptide is presented by HLA class-I molecule**
2. Presented peptide is recognized as non-self

$$s_k \propto \frac{1}{e_k}$$

s_k → susceptibility of individual k

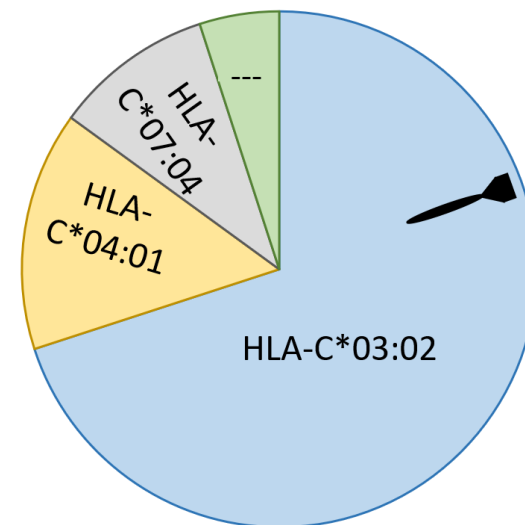
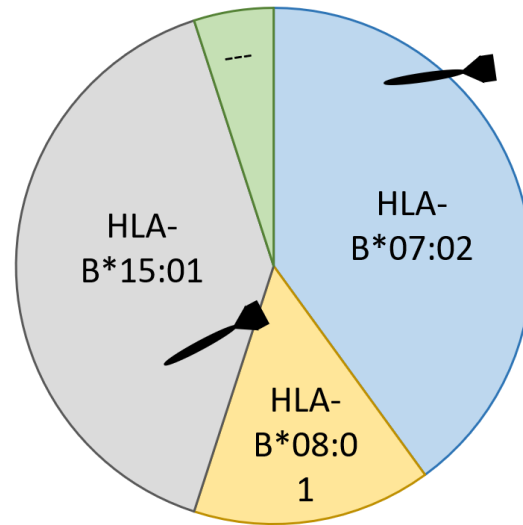
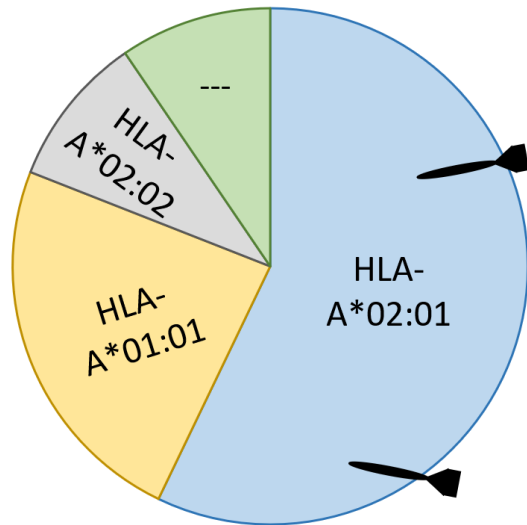
e_k → number of viral epitopes presented by individual k



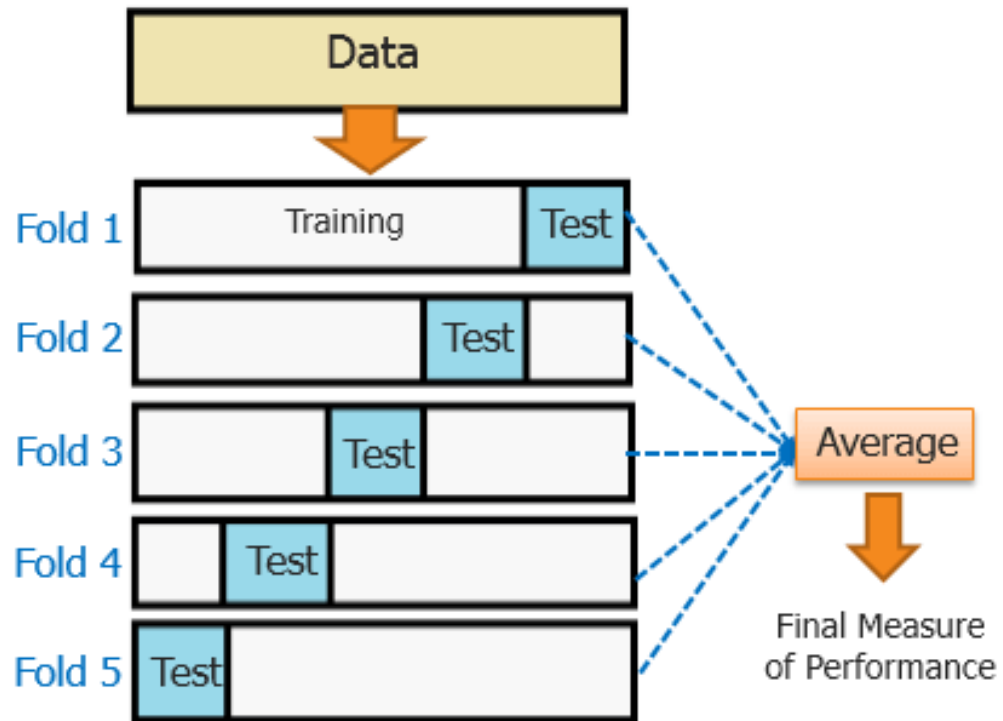
Individual = HLA genotype

- A person has 6 HLA class-I alleles (two each of A, B and C)
- Generate HLA genotypes $A_1 A_2 B_1 B_2 C_1 C_2$ based on single allele frequencies

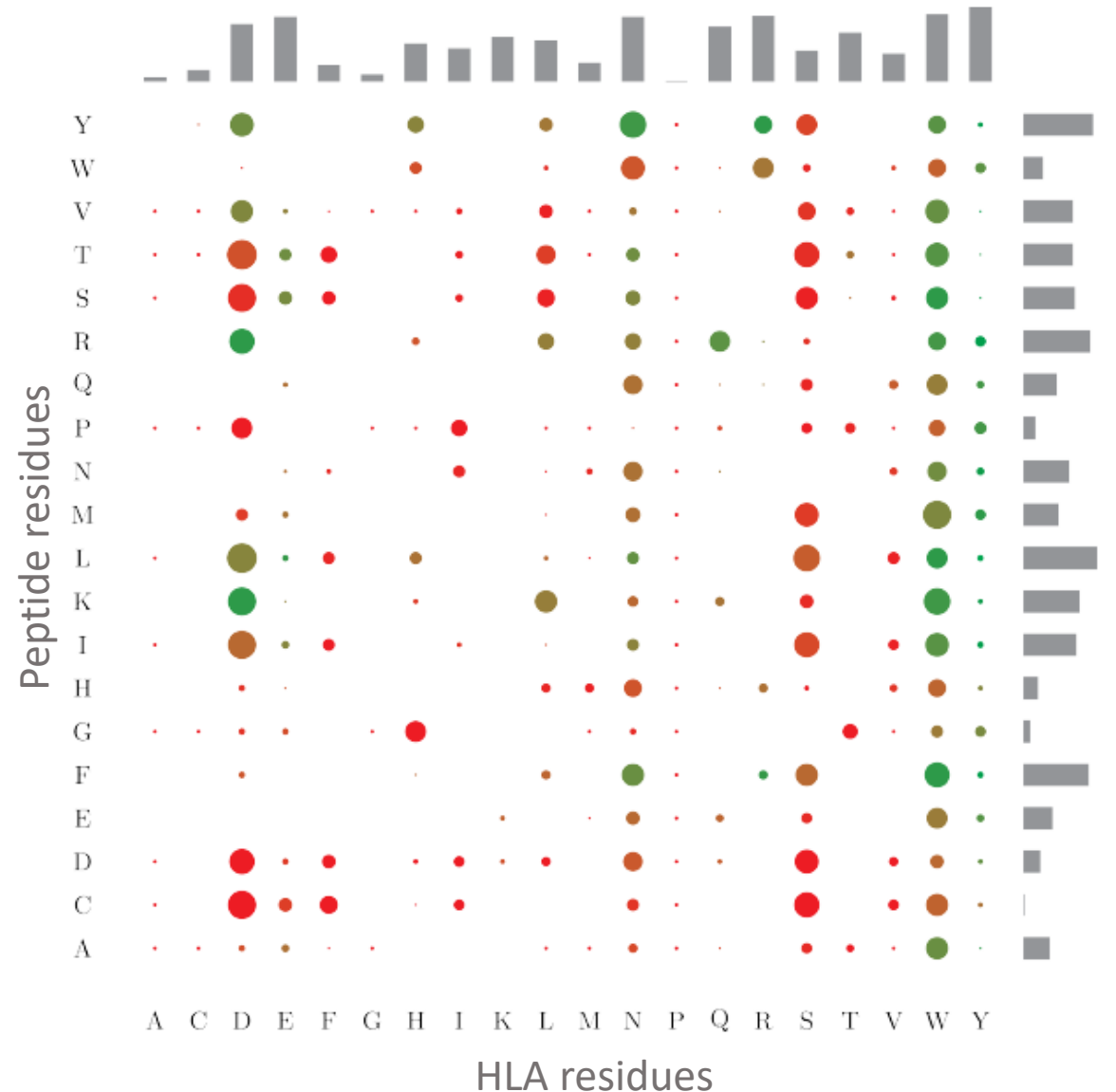
$$e_k = \sum_{\text{alleles in HLA genotype}} \text{epitopes}$$



Predicting epitopes

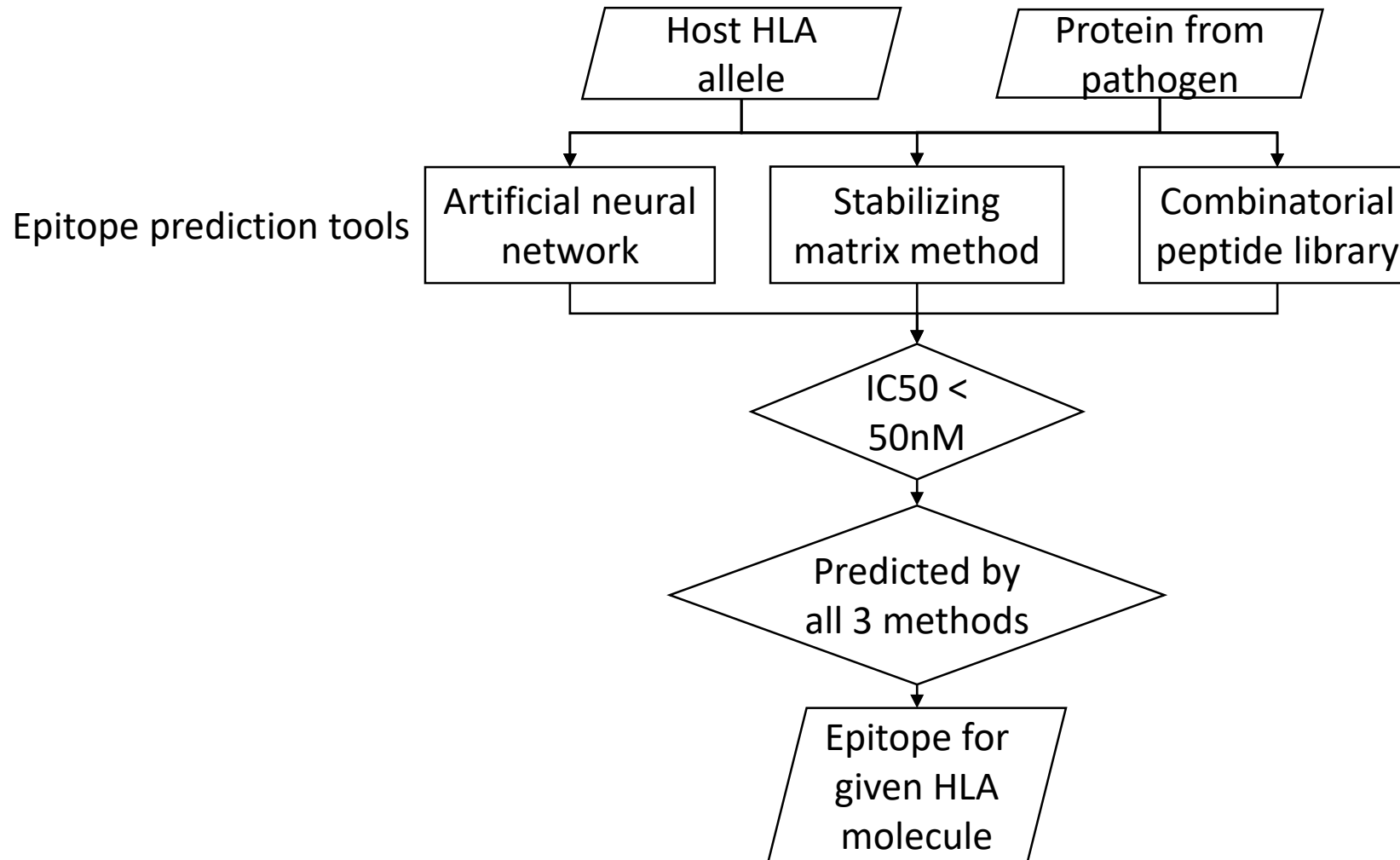


Learning based methods

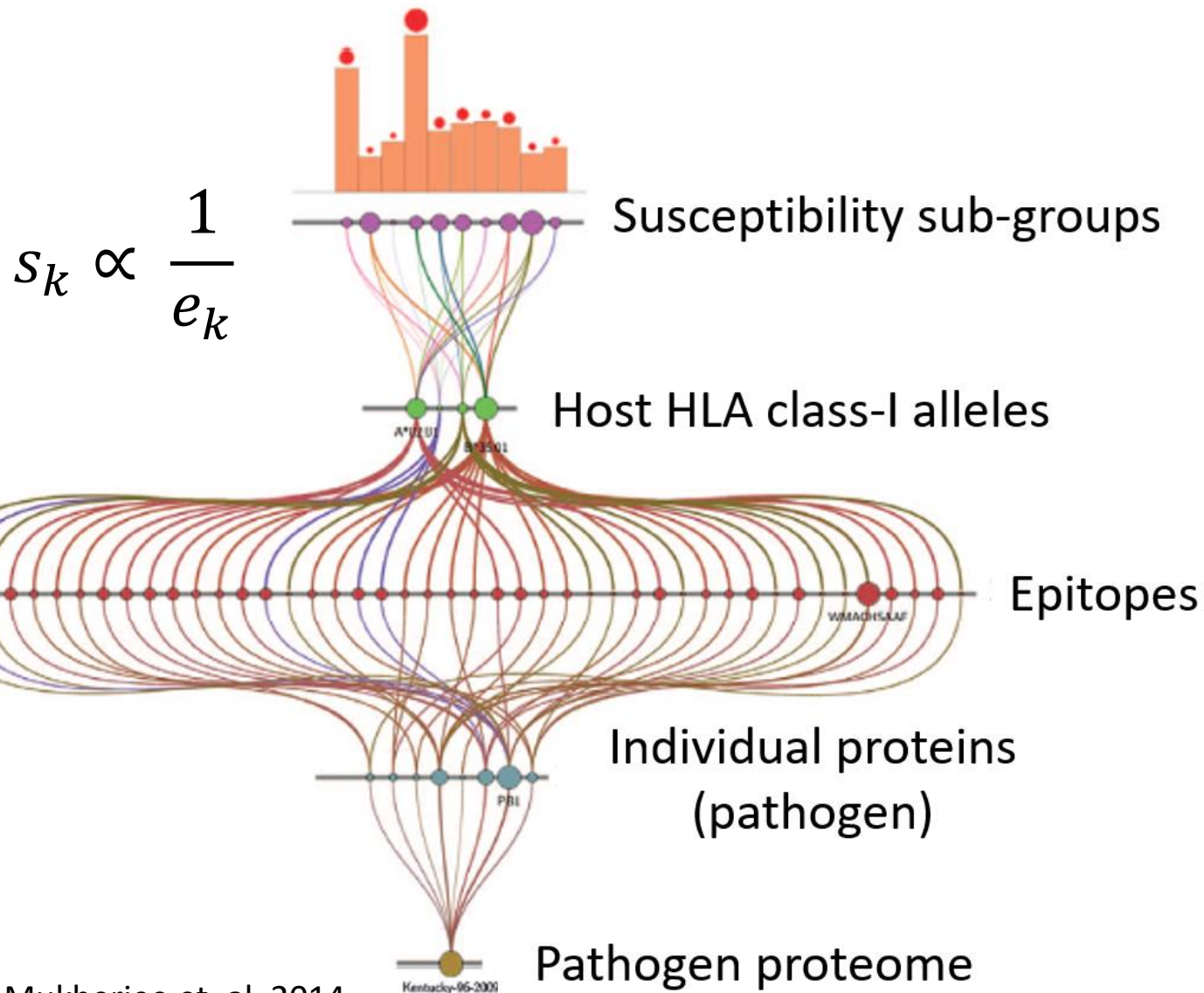


Energy based methods

Predicting epitopes



Forming susceptibility sub-groups



- ✓ Number of susceptibility sub-groups (m)
- ✓ Size of each sub-group (x_i)
- ✓ Beta for each sub-group (β_i)

Value of β_i

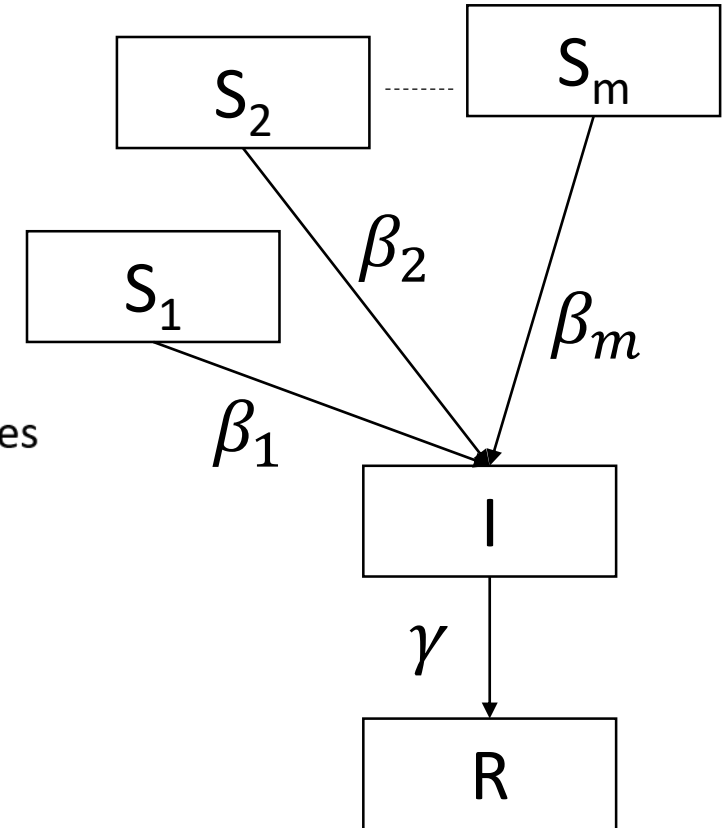
$$\beta_i = \alpha c s_i = \alpha c z \frac{1}{e_i} = \gamma \frac{1}{e_i}$$

Infectiousness of individual in I
 $\alpha \in [0,1]$
 $[\alpha] \rightarrow \textit{dimensionless}$

Average number of contacts per individual per unit time
 $[c] \rightarrow \textit{person}^{-1}\textit{time}^{-1}$

Susceptibility
 $s_i \in [0,1]$
 $[s_i] \rightarrow \textit{dimensionless}$

No. of epitopes



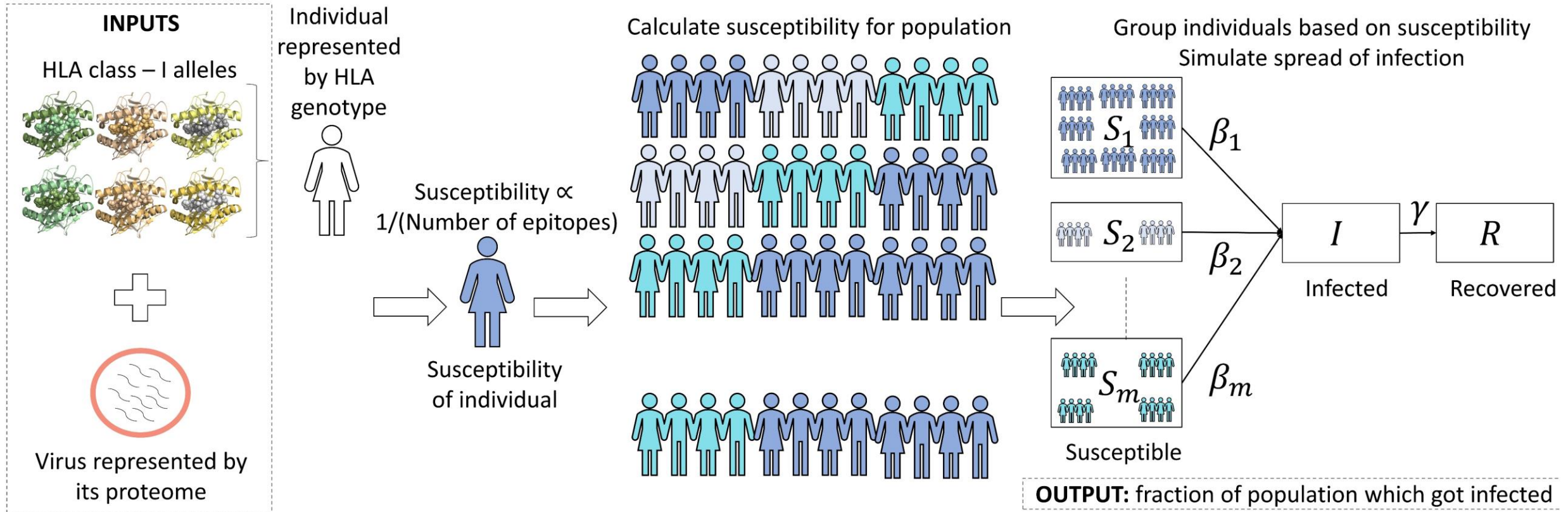
Estimating y

- Quantity β can be calculated as a weighted average of the β_i values

$$\beta = \sum_{i=1}^m x_i \beta_i = \sum_{i=1}^m x_i y \frac{1}{e_i} = y \sum_{i=1}^m x_i \frac{1}{e_i}$$

- Experimentally determined β
 - (Mexico City Mestizo pop 2, A/Mexico/LaGloria-8/2009)
- Calculate m , x_i and e_i for that ethnicity and viral strain and then estimate y

Incorporating genetic heterogeneity



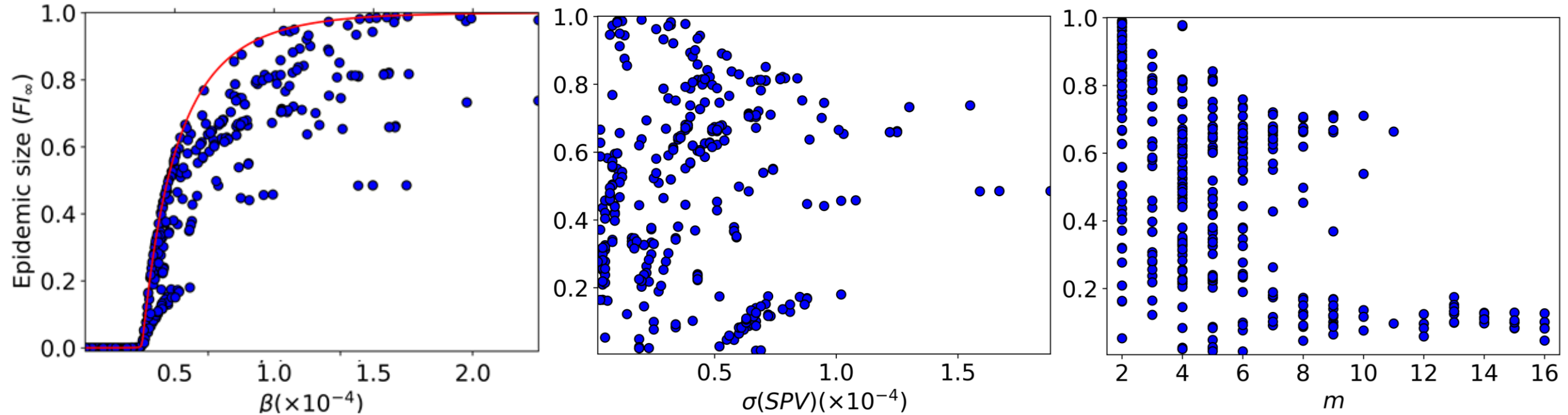
$$SPV(E, V) = (\underbrace{\beta_1, \dots, \beta_1}_{N_1}, \underbrace{\beta_2, \dots, \beta_2}_{N_2}, \dots, \underbrace{\beta_m, \dots, \beta_m}_{N_m})$$

Susceptibility Profile Vector

Data and predictions

- Inputs
 - HLA allele frequencies for 61 ethnicities (The Allele Frequency Net Database)
 - H1N1 proteomes for 166 strains (NCBI)
 - 81 isolated in 2009
 - 85 isolated in other years
- Predicted values
 - Epidemic size = $\frac{R(\infty)}{N}$

No single parameter predicts epidemic size



- Certain characteristics of the SPV, taken together, correlate well with epidemic size
- Diversity in susceptibility protects the population

Role of genetic heterogeneity in determining the epidemiological severity of H1N1 influenza.

PLoS computational biology 14.3 (2018)

High risk alleles are not enough

- Frequency of HLA-A*24 correlated with mortality rate due to pandemic H1N1
- But this correlation does not hold true in general

Ethnicity	Allele frequency rank	Frequency	Average epidemic size
USA Alaska Yupik	1	58%	0.68
Japan Central	2	38%	0.009
Japan pop 3	3	36%	0.02

Host heterogeneity is important

- Indigenous ethnicities experienced more severe epidemics than their non-indigenous counterparts during the 2009 pandemic
- **USA Alaska Yupik** is always predicted to have a worse epidemic than non-indigenous ethnicities from the USA, irrespective of the strain

Host heterogeneity alone is not enough

- Australia Cape York Aborigine: average epidemic size = 0.14
- Australia Yuendumu Aborigine: average epidemic size = 0.08
- For strains isolated in Australia, this trend is reversed

Ethnicity	Viral strain	m	$\beta \times 10^{-4}$	Epidemic size
Australia Cape York Aborigine	A/Auckland/1/2009	3	0.33	0.006
Australia Cape York Aborigine	A/Auckland/597/2000	3	0.19	0.0002
Australia Yuendumu Aborigine	A/Auckland/1/2009	1	0.5	0.57
Australia Yuendumu Aborigine	A/Auckland/597/2000	1	0.28	0.0006

Conclusions and Ongoing work

- Both host and pathogen heterogeneity are important
- CD8+ T cell response to incorporate both host and pathogen data
- More accurate predictions of epidemic size
- Greater diversity in susceptibilities leads to smaller final epidemic sizes



Ongoing work – Spatial heterogeneity (**Poster P5**)

Thank you

Posters P5, P6

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