Adaptation in a varying fitness landscape

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Motivations

- Modeling viral evolution in adaptation to host immune response

Evolving Quasispecies Behavior

- Genetic Drift of Influenza A virus during Interpandemic periods

- Intra-host evolution of HIV in asymptomatic periods.

Evolution of the human influenza A virus in Interpandemic periods:

Genetic Drift

Hemagglutinine (HA) and Neuraminidase (NA) surface proteins of the virus : main antigenic sites
High rate of non-synonymous substitutions. Escape from the Immune Systems

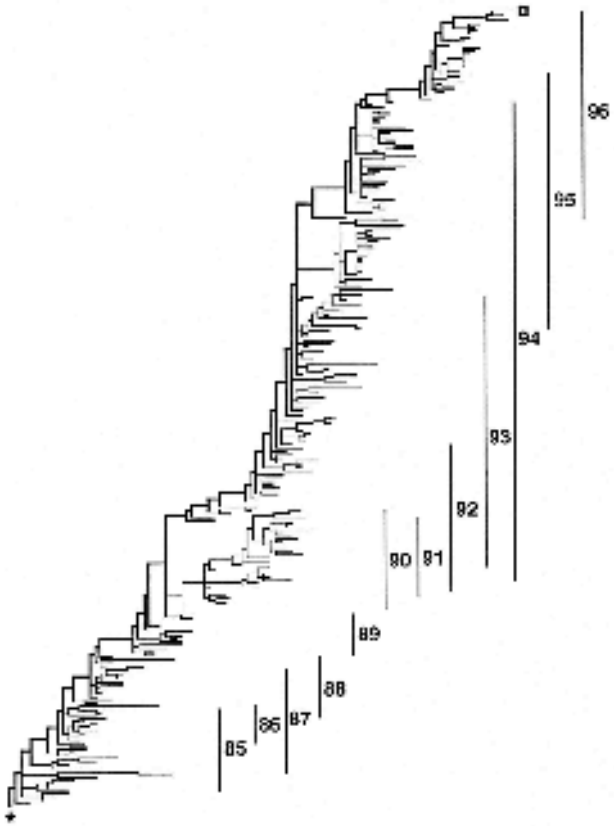
High level of morbidity maintained by the fast evolution of the virus. 5-15 % of human population
is infected each year

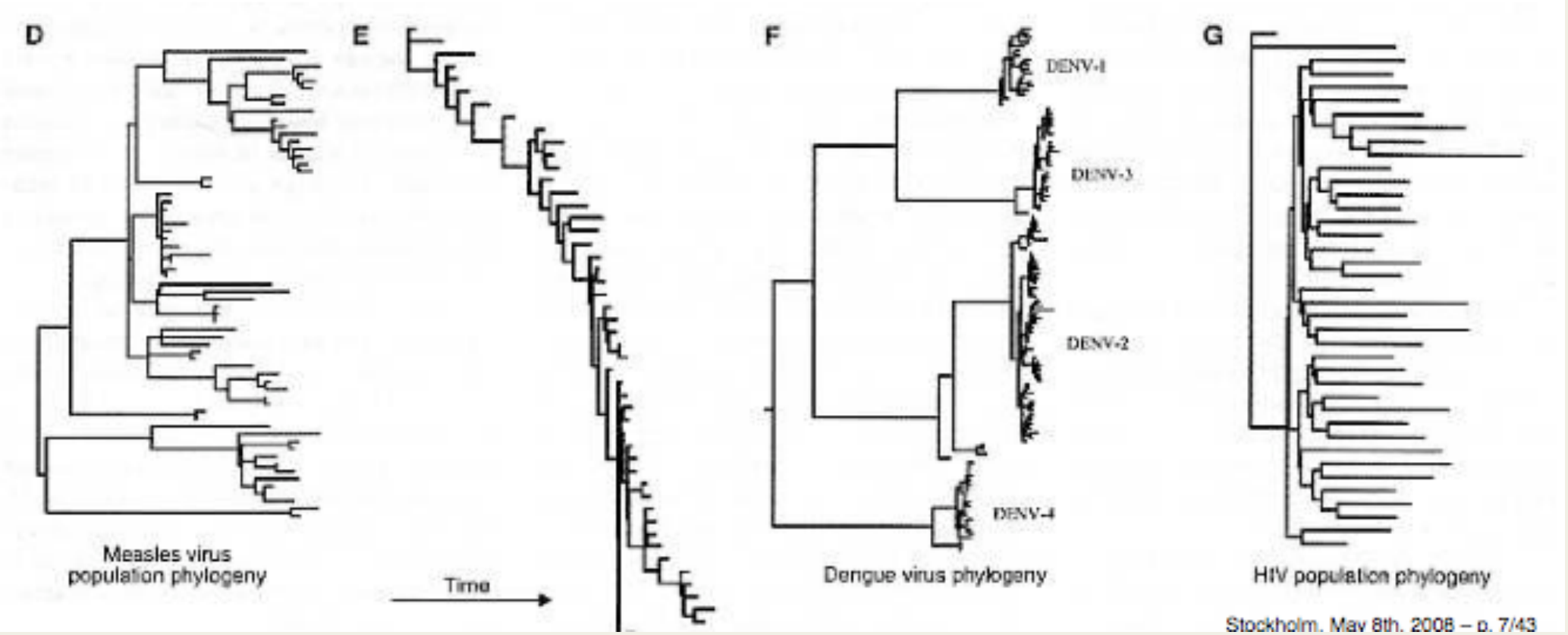
Vaccine has to be changed every year.

At each instant of time there is a vell defined subtype

Flu: type A, subtype H3N2, gene HA1

Fitch, Bush, Bender and Cox, 1997

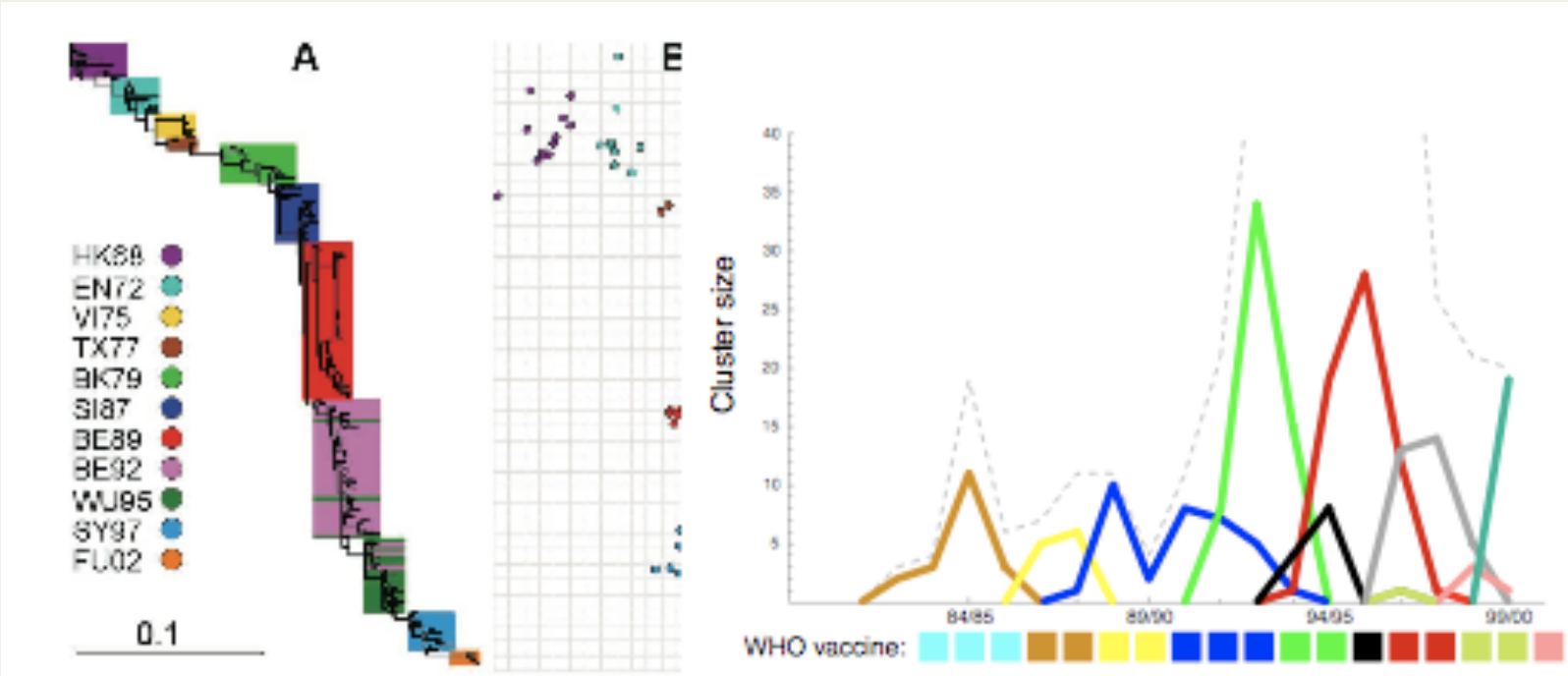



D
E
F
G
DENV-1
DENV-3
DENV-2
DENV-4
Measles virus
population phylogeny
Time
Dengue virus phylogeny
HIV population phylogeny

Genetic Evolution : Gradual

Antigenic Properties : Punctuated

Strains are clusterized in time



D. J. Smith et al (2004)

The Evolutionary Puzzle

•Advantage for differentiation
•Yet at each time a well defined dominant strain (vaccination is possible) (Eigen's quasispecies)

•Why there is not proliferation of different strains with different genetic and antigenic properties ?

•Mechanisms for Evolving Quasispecies behavior

The Devil's alternative:
Simple models give proliferation of viral strains or extinction

- Models : Evolutionary and Epidemiological aspects

Modeling the Epidemic spreading in the host population in presence of immune memory

Individual based model

transmission in presence of Acquired Immunity and Viral Mutations

Numerical Simulations ----- Large number of parameters ------

- Short term a-specific immunity (Ferguson N M, Galvani A P and Bush R M, 2003)
- Heterogeneity in the transmission (S.F. M.Lassig, L. Peliti, F. Tria 2005)

Simplifications:

A. Constant viral population size
B. Effective model for acquired immunity

Fisher-Wright evolution model

S "genotype" W_S fitness

Individuals reproduce proportionally to fitness

Prob. of being daughter of « i »: $\frac{W_{S_i}}{\sum_{j=1}^{N} W_{S_j}}$

Mutations: in a reproduction event there is probability μ of mutation.

$Q_{S \to S'}$ Prob. that a mutation from S gives S'.

The House of Cards

W_S Chosen randomly from a distribution $\rho(W)$

Infinite allele model $Q_{S \to S'} = 1/\mathcal{N} << 1$

Each time there is a mutation a random fitness is drawn.

Effective Model for Acquired Immunity

The fitness of a strain "S" decreases in reason of the number of individuals $n_t(S)$ with that strain:

$$W_S(t+1) = W_S(t)\lambda^{n_t(S)}$$

$$\lambda < 1$$

Case $\lambda = 1$

Infinite population limit: $N \longrightarrow \infty$

$x_t(W)$ fraction of individuals with fitness “W “at time“t”

$$x_{t+1}(w) = \frac{w}{\langle w \rangle} x_t(w)(1-\mu) + \mu\rho(w)$$

Neglect fluctuation in fitness occupation numbers.

The House of Card: (1) Infinite population

If $\rho(W)$ has a compact support: $w < w_{Max}$

Stationary distribution

$$x(w) = \frac{\mu\rho(w)}{1-(1-\mu)\frac{w}{\langle w\rangle}}$$ Bose-Einstein

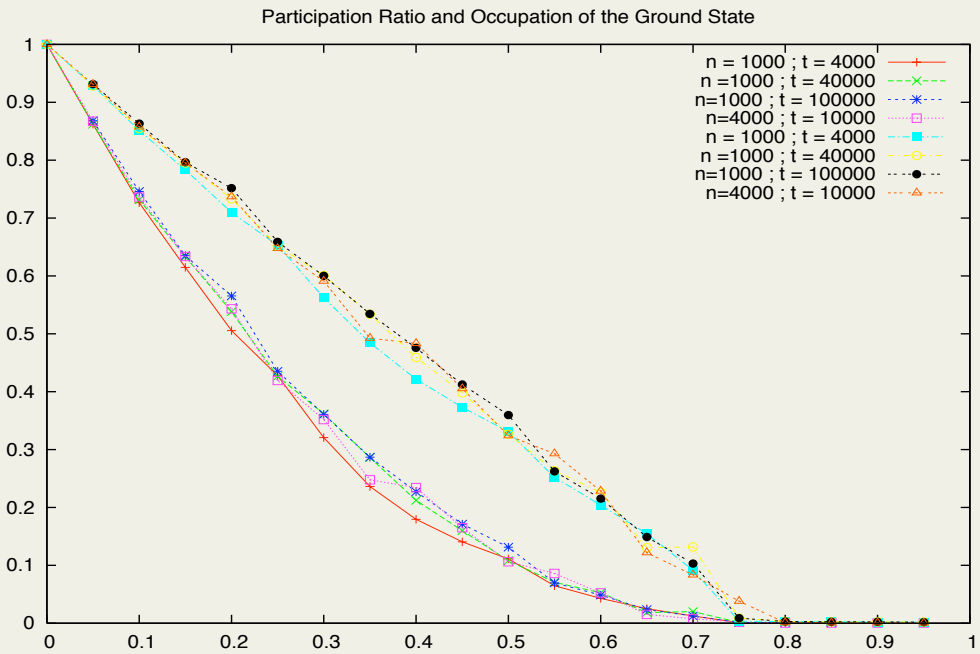
If $\int_0^{w_{Max}} \frac{\rho(w)}{1-\frac{w}{w_{Max}}}\, dw < \infty$ a condensation (error threshold)

separates a well adapted phase where a finite fraction of individuals have $w = w_{Max}$ from a not adapted phase

Condensate + non-condensate = Quasispecies

Finite N: "dynamical condensate" N and t dependent Error-Trheshold

If $\rho(W)$ has not a compact support: No error threshold for infinite N: effective error threshold for finite N.



$$\rho(w) = \frac{e^{-\frac{1}{2a^2}log^2(w)}}{wa\sqrt{2\pi}}$$

Condensate fraction:

$$\nu = 1 - \mu/\mu_c$$

$$\mu_c^{-1} = \int_0^{w_M} \frac{\rho(w)}{1 - w/w_M(t)}$$

Punctuated equilibria (aging state)

$$w_M(t) \approx exp(\sqrt{2a^2 Log(N\mu t)})$$

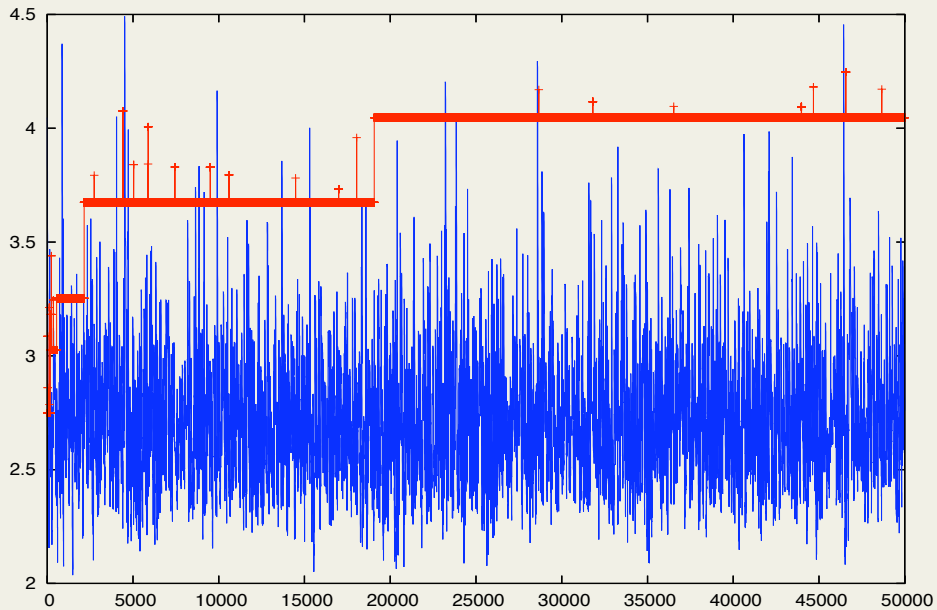
Record process

$$\lambda = e^{-h/N}$$

Numerical Simulations for $h > 0$

A non zero “h” introduces a time scale into the system: Stationarity

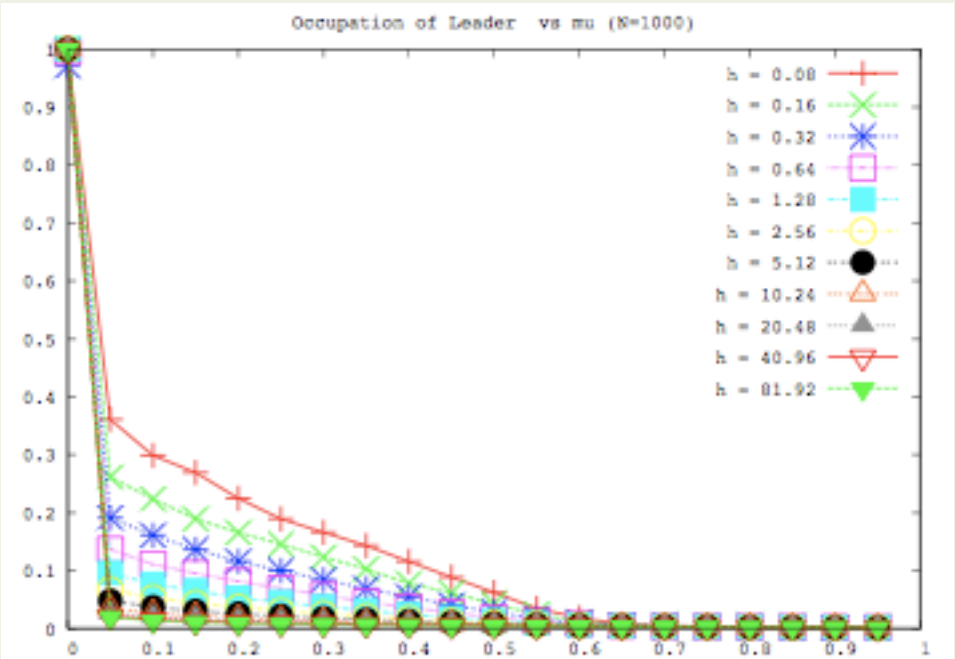
Max fitness vs t
for N=1000, a=.3
mu=0.1
h=0 (red)
h=0.01 (blue)



Phase diagram

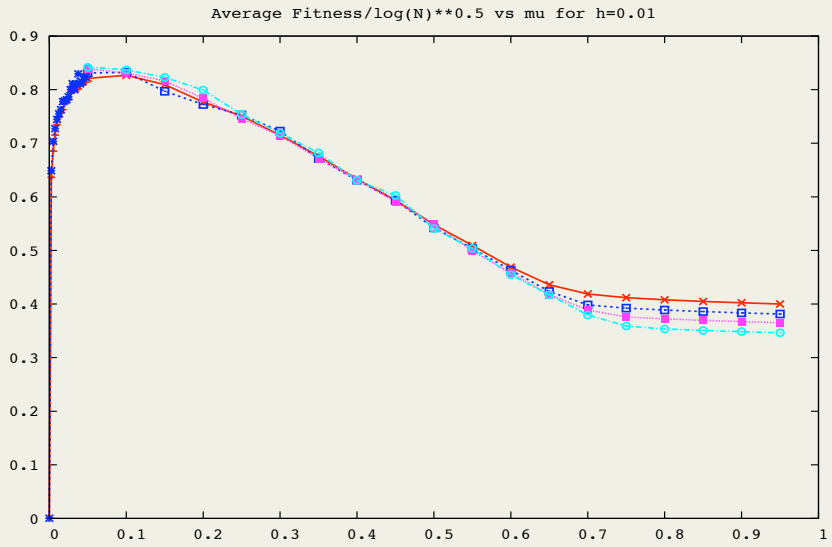
Existence of a Dynamical Condensed well Adapted Phase
Separated from a poorely adapted phase.

MOS most occupied strain
Leader or Champion

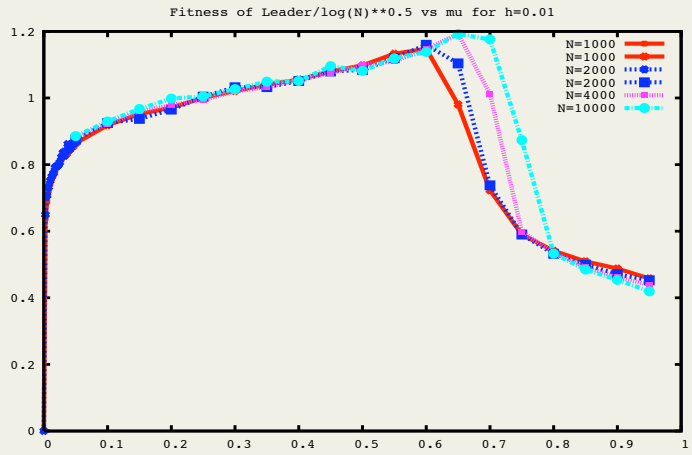


Fitness as a function of mutation rate

Average fitness has a Max for a non zero mutation rate.



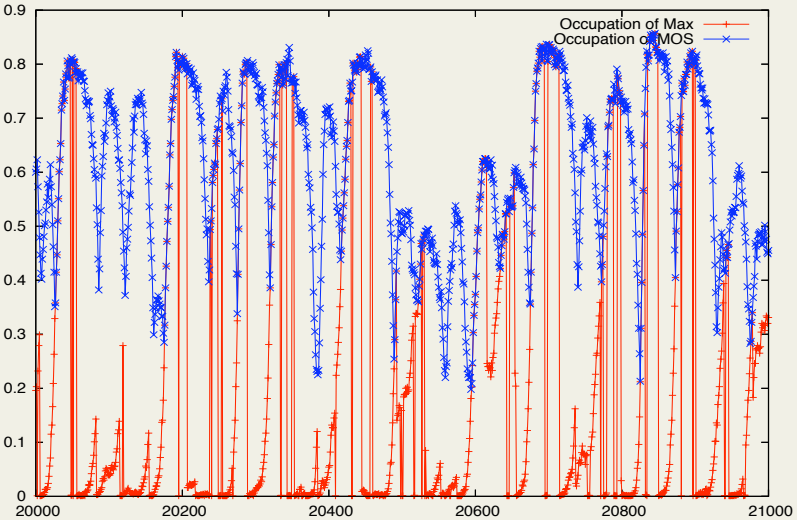
Fitness of MOS has a max in correspondence of the error threshold

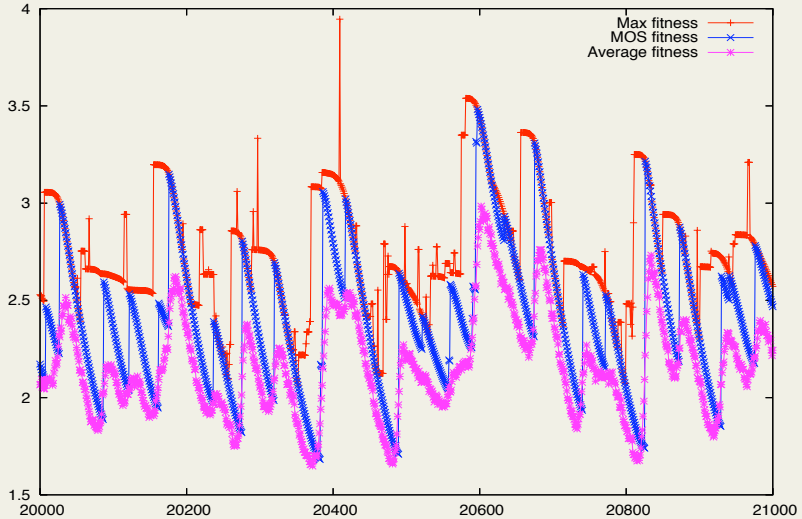


Dynamics in the condensed phase: Evolving Quasispecies.

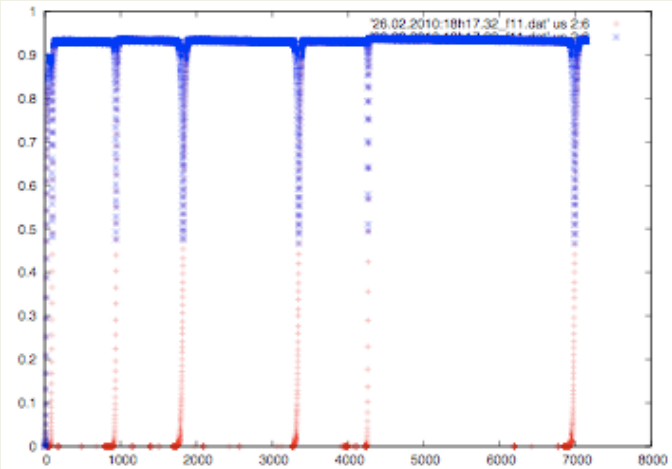
Substitution of MOS

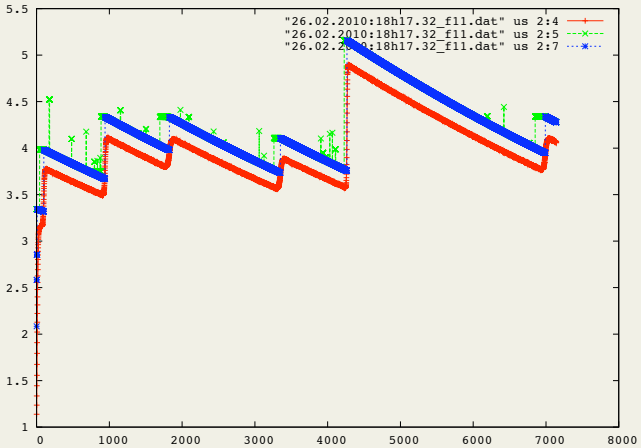
mu= 0.1 ; N = 1000 ; h = 0.01





mu= 0.05 ; N = 40.000 ; h = 0.01

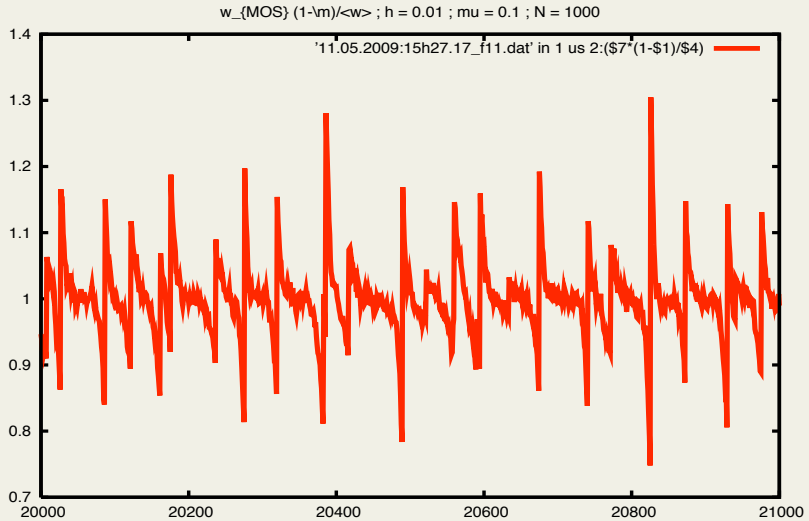


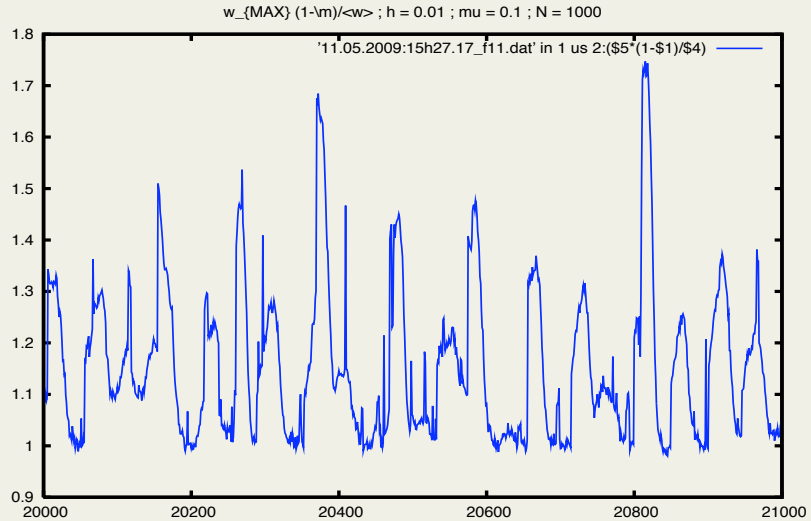


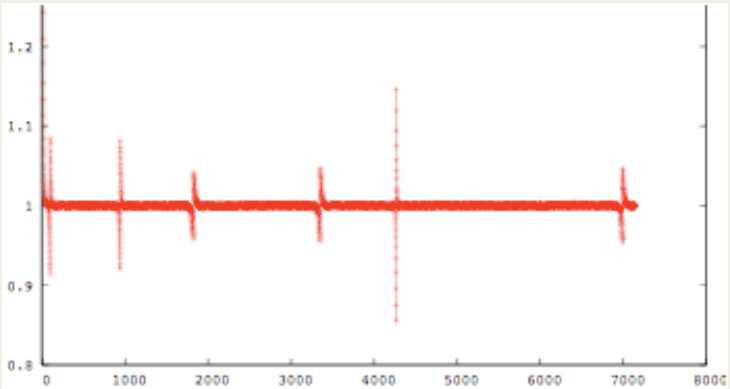
Reproduction rate of Mos and Max.

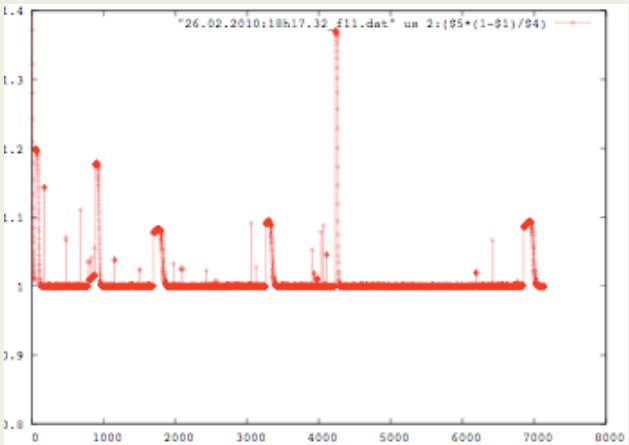
$$w(1-\mu)/\langle w \rangle$$

Quasi-periodic oscillations





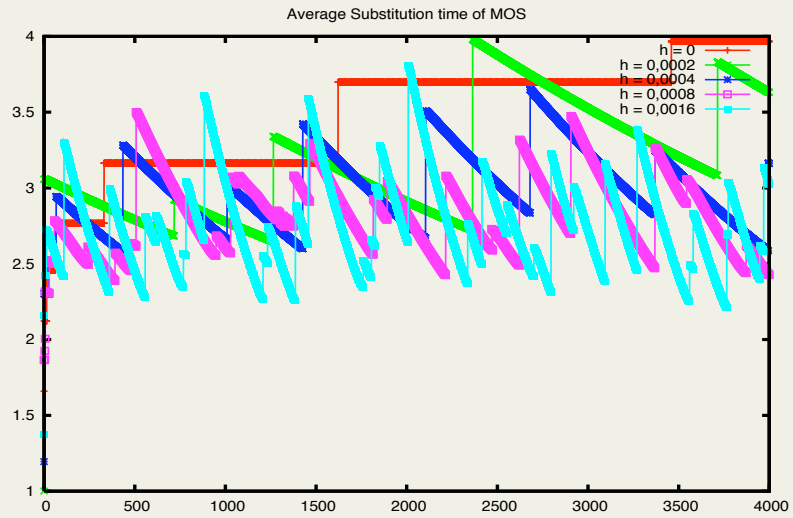




Time Scales

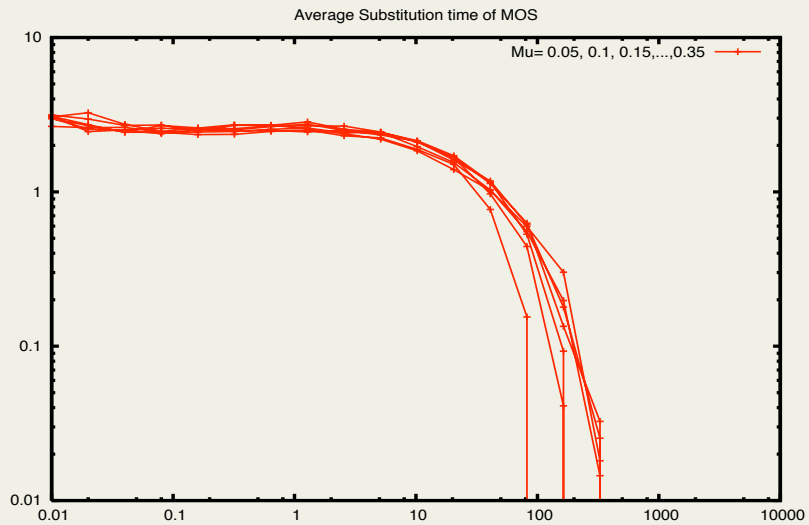
Characteristic Decay time of MOS fitness:

$$t_{decay} = C/h$$



Substitution time of MOS

$$t_{sub} = C/h^{1/2}$$



C could be Log(mu).

The Champion Process:

Champion in charge $w_t = w_0 \lambda^t$

Challenger $w \longrightarrow \rho^*(w)$

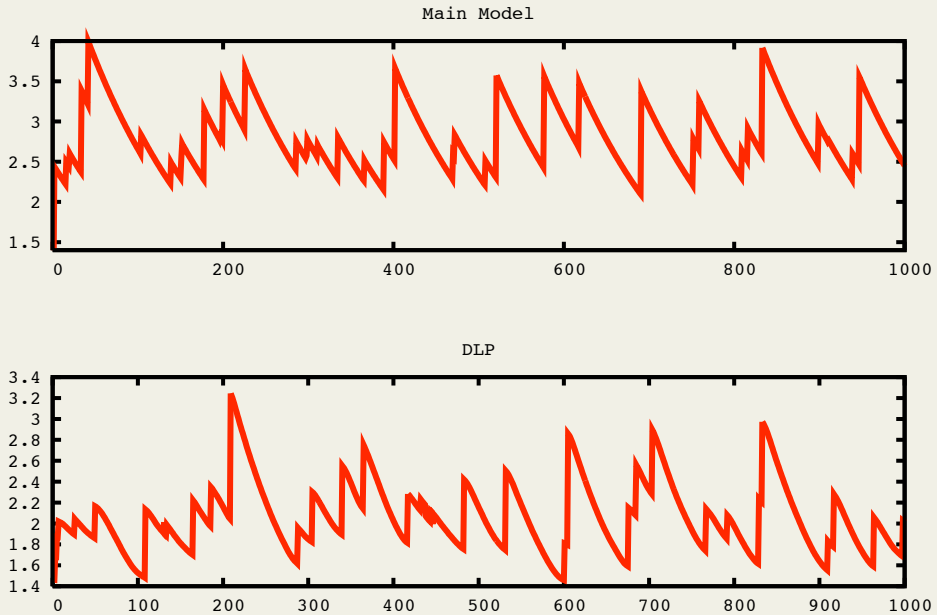
Substitution if $w > w_t$ (or with a prob.)

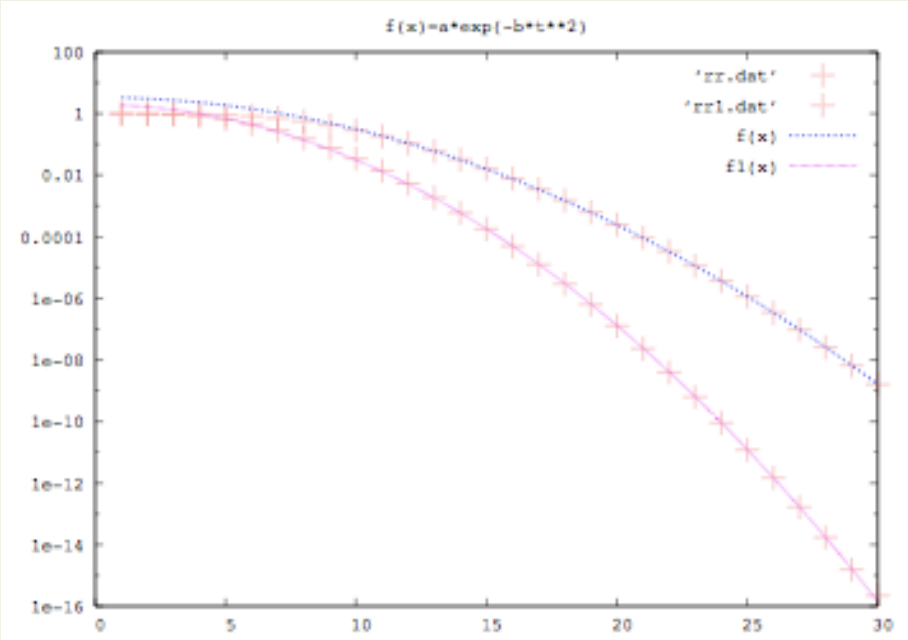
Probability of survival for more then t time steps of a leader with original fitness w_0

$$P_>(t|w_0) = \prod_{s=1}^{t} \int_0^{w_0 \lambda^s} dw \; \rho^*(w)$$

$$\rho^*(w) = \mu N \rho(w)\, \mathrm{e}^{-\mu N \int_w^\infty dw'\ \rho(w')}$$

Distribution of the Max of μN variables distributed accroding to $\rho(W)$





$$P_{>}(t|w_0) \sim \lambda^{t^2} f(w_0)$$

$$\lambda = e^{-hn^*} \qquad t_{sub} = C/h^{1/2}$$

Conclusions

Mechanism for evolving quasispecies behavior

Heterogeneity in the transmission

Moderate fitness degradation does not destroy the Error threshold.

Competition leads to stationary behavior.