

ViroLab

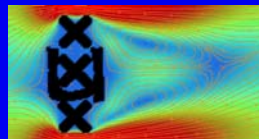
A Virtual Laboratory for Infectious Diseases



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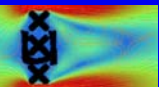
Vision Quote

"During the next decade, the practice of medicine will change dramatically, through genetically based diagnostic tests and personalized, targeted pharmacologic treatments that will enable a move beyond prevention to pre-emptive strategies."

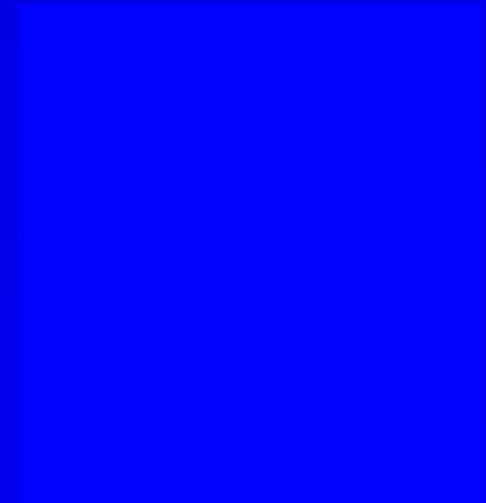
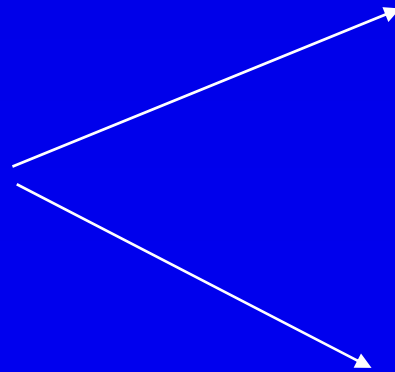
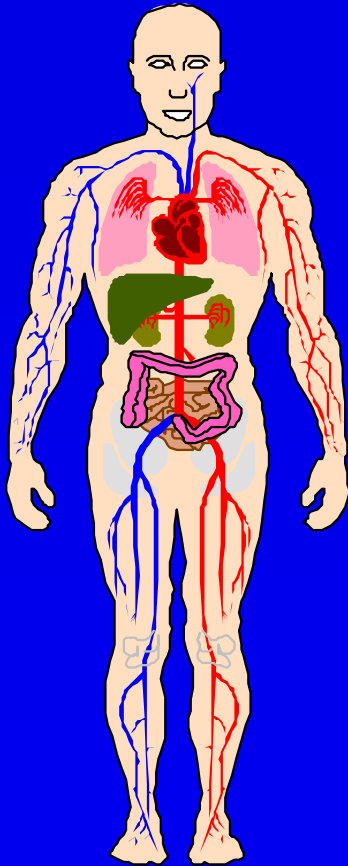
Senate Majority Leader, Bill Frist, MD

"Health Care in the 21st Century"

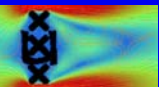
New England Journal of Medicine, Jan. 2005



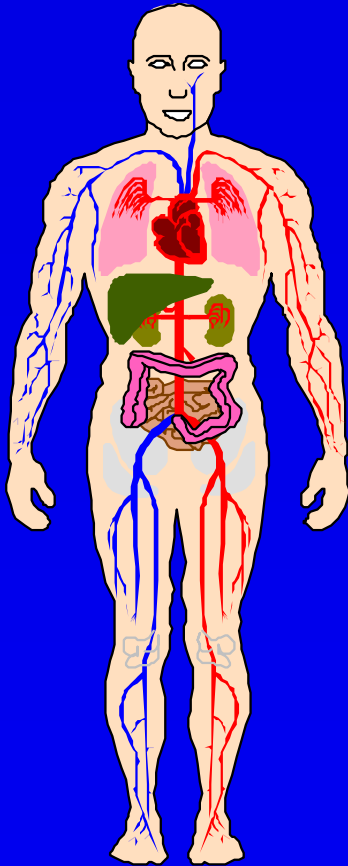
All the Paradigms



In Vivo



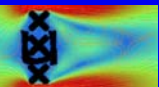
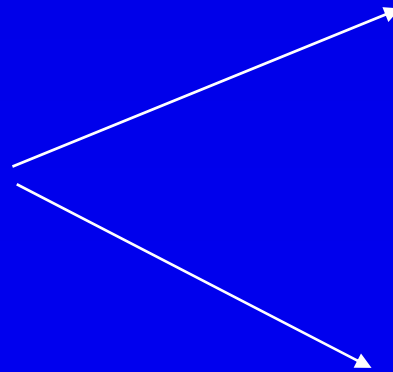
All the Paradigms



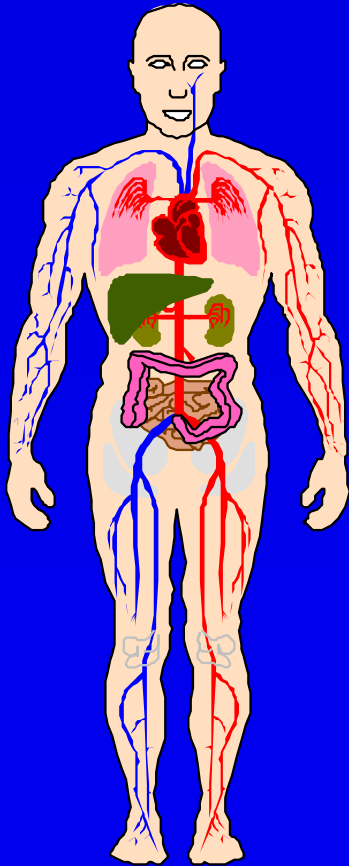
In Vivo



In Vitro



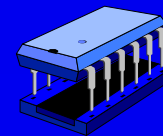
All the Paradigms



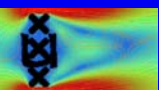
In Vivo



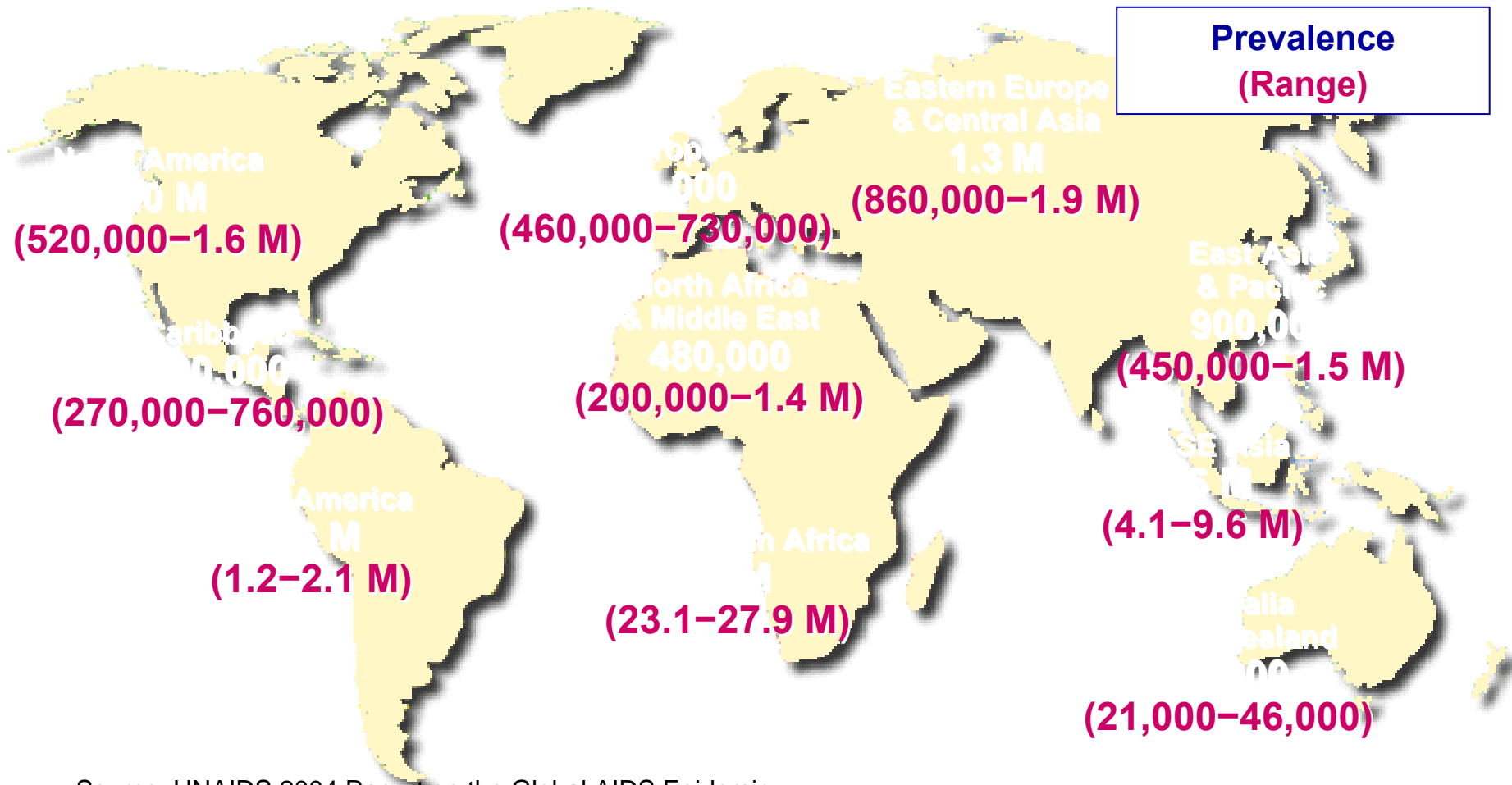
In Vitro



In Silico



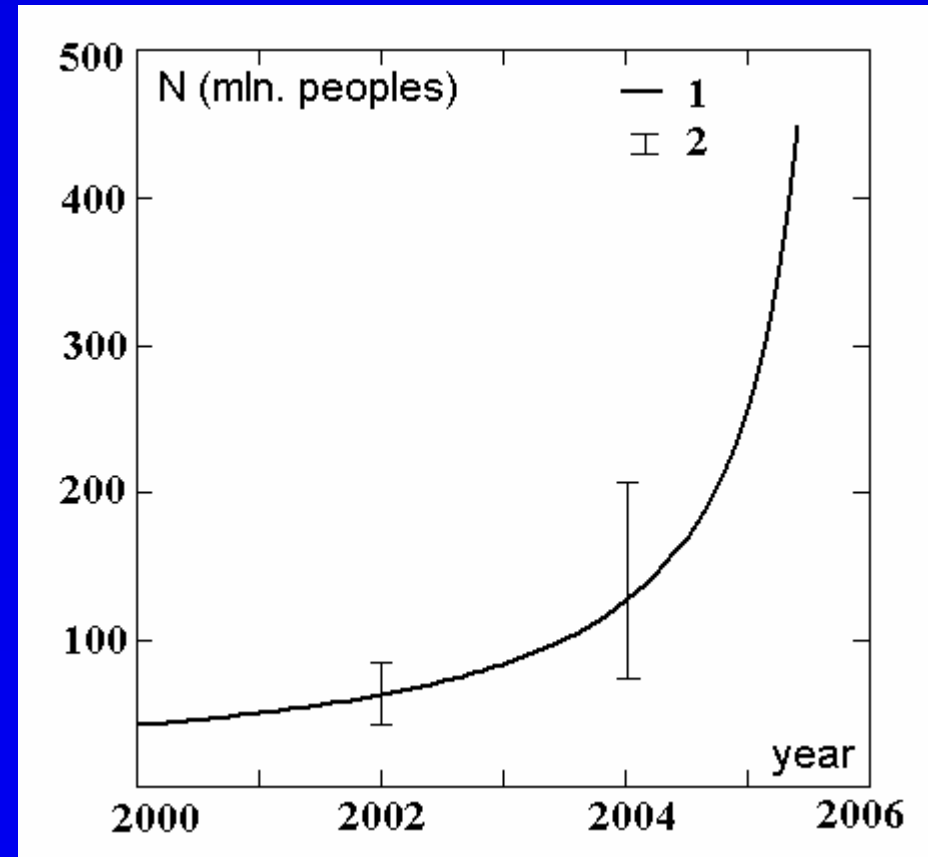
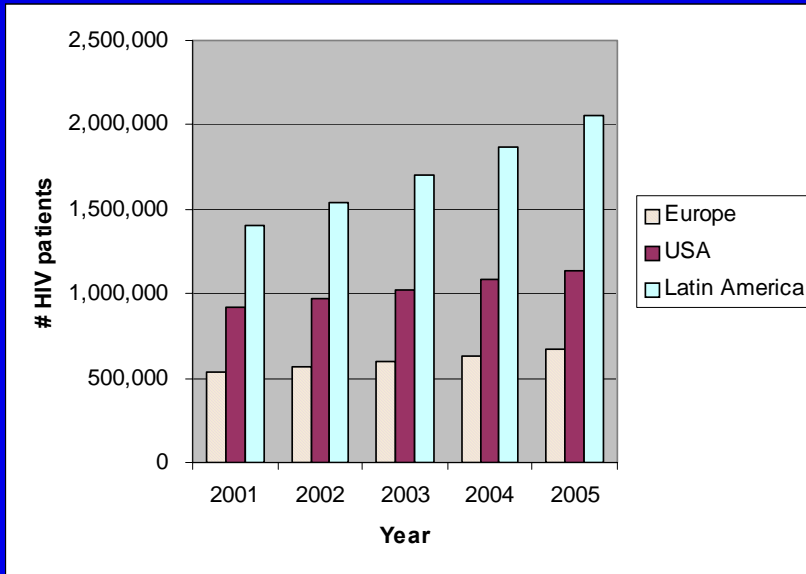
The AIDS pandemic: Adults and children living with HIV/AIDS, end 2003



Source: UNAIDS 2004 Report on the Global AIDS Epidemic

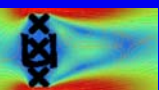
- 4.8 M new HIV infections in 2003
- 2.9 M deaths due to HIV/AIDS in 2003
- 38 M living with HIV/AIDS; 50% females

HIV progression

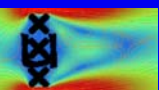
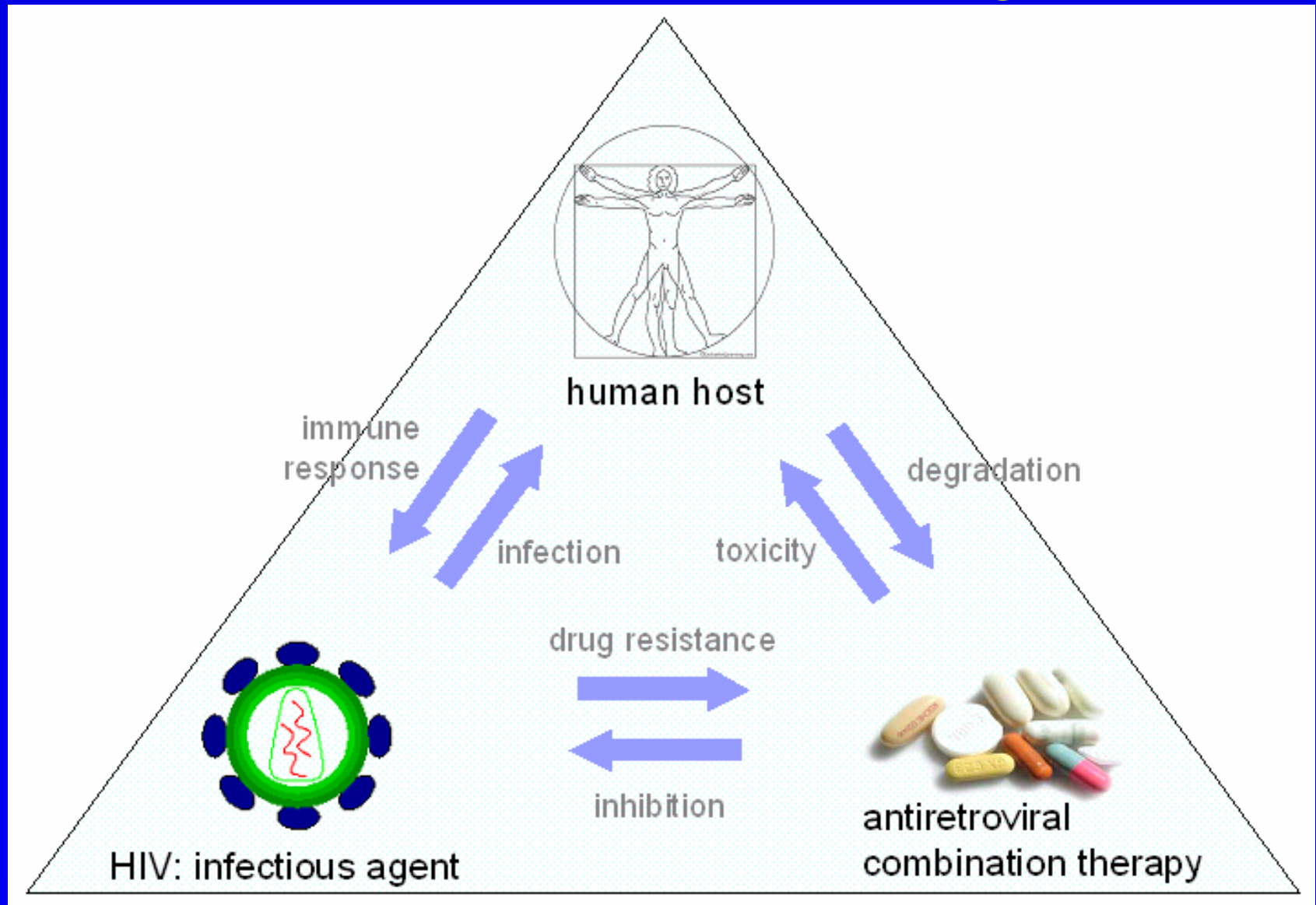


Slout et al., JCMC vol. 19, nr 4-5 2005.

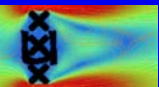
Qualitative forecast of HIV-1 population grows.
1 – mean value (7), 2 – 90% confidence interval.



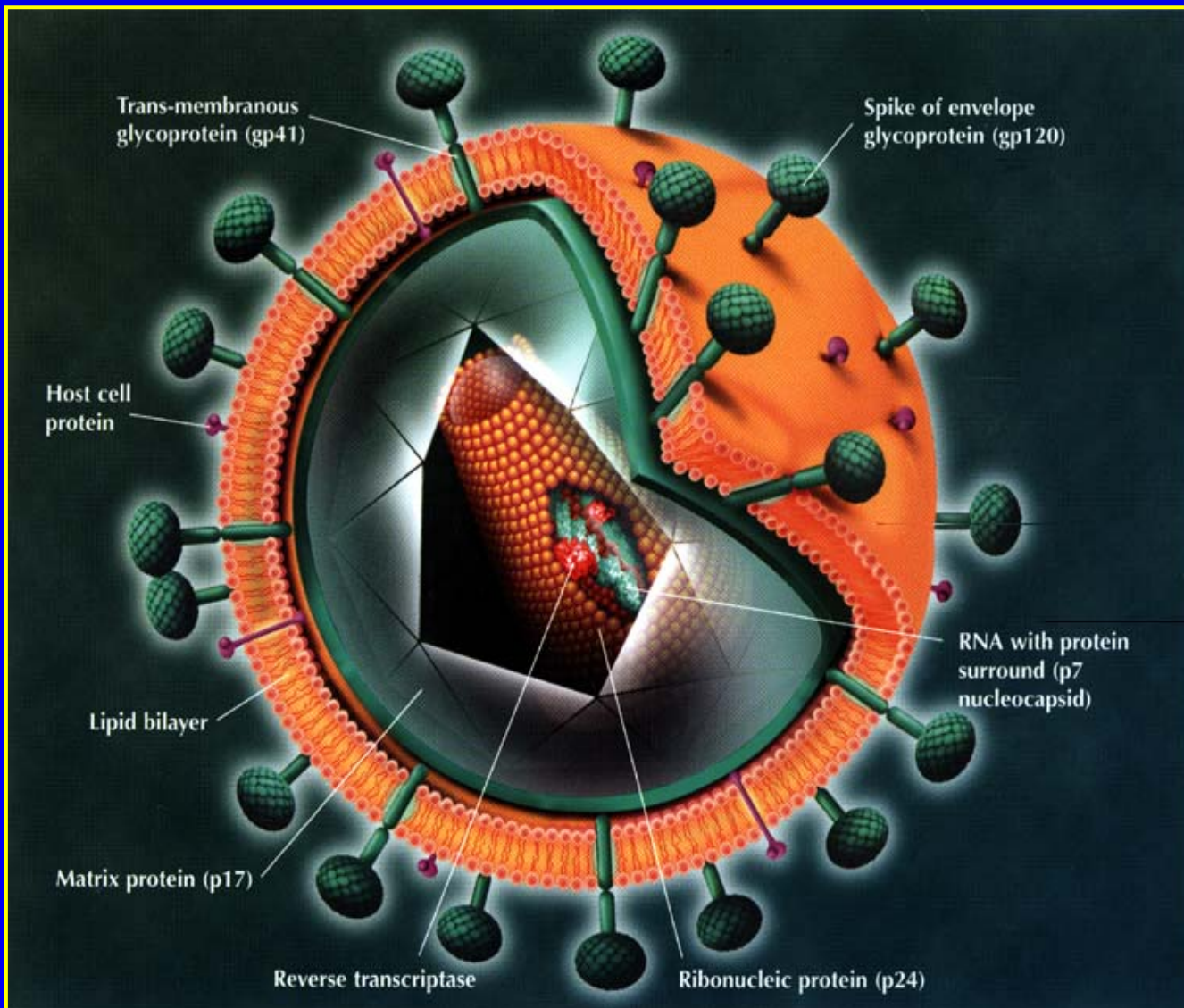
The complex interplay in HiV



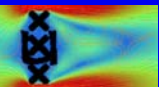
A few words on the Molecular Basis of HIV-1



Human immunodeficiency virus



- 10^9 new viruses produced every day
- RT makes an error during each transcription
- Due to the high error rate, multiple mutations



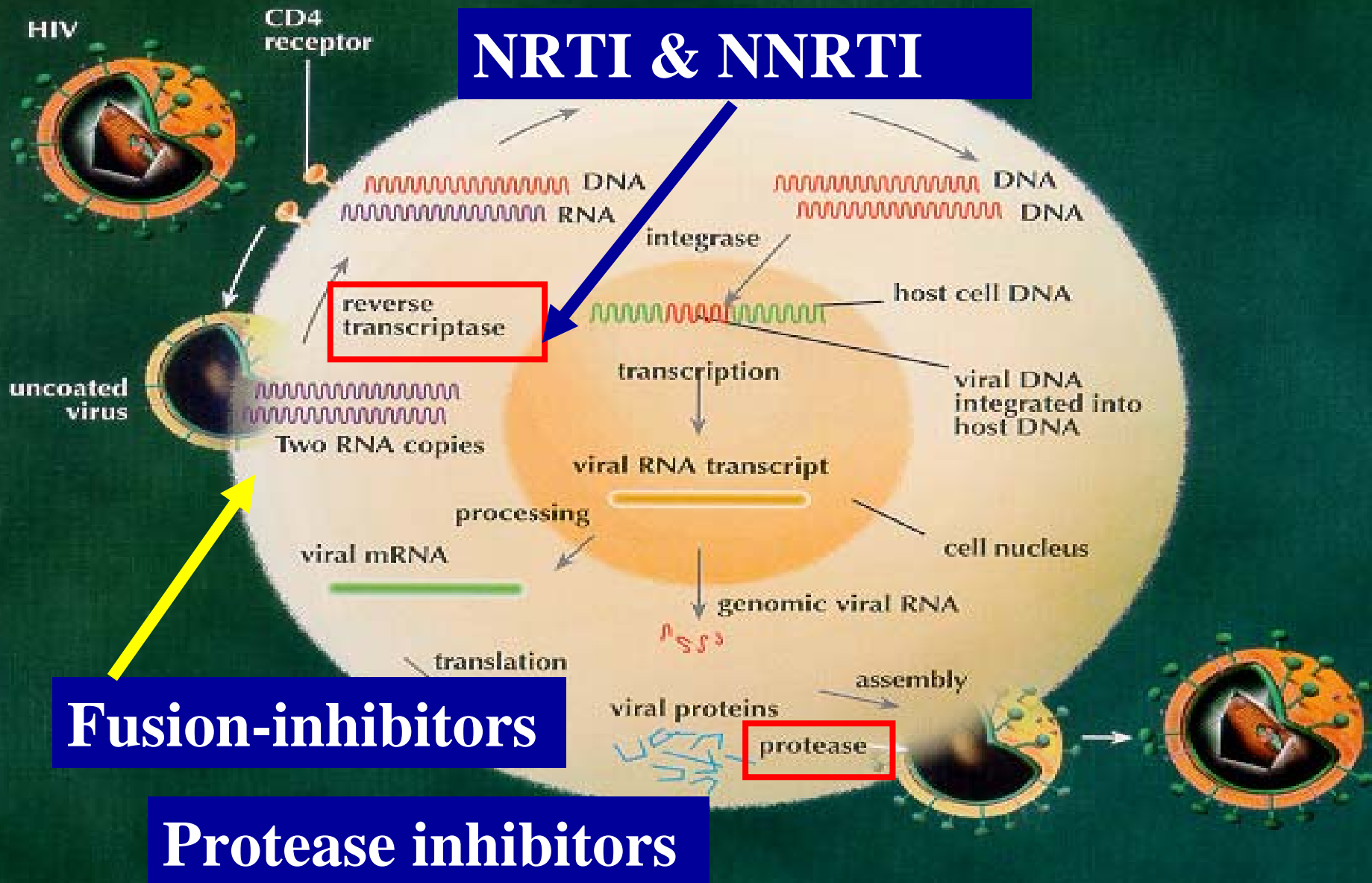
Virus Replication

General transcription, translation,
and genome replication
mechanisms of some viruses

CONTENTS



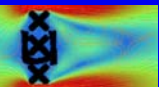
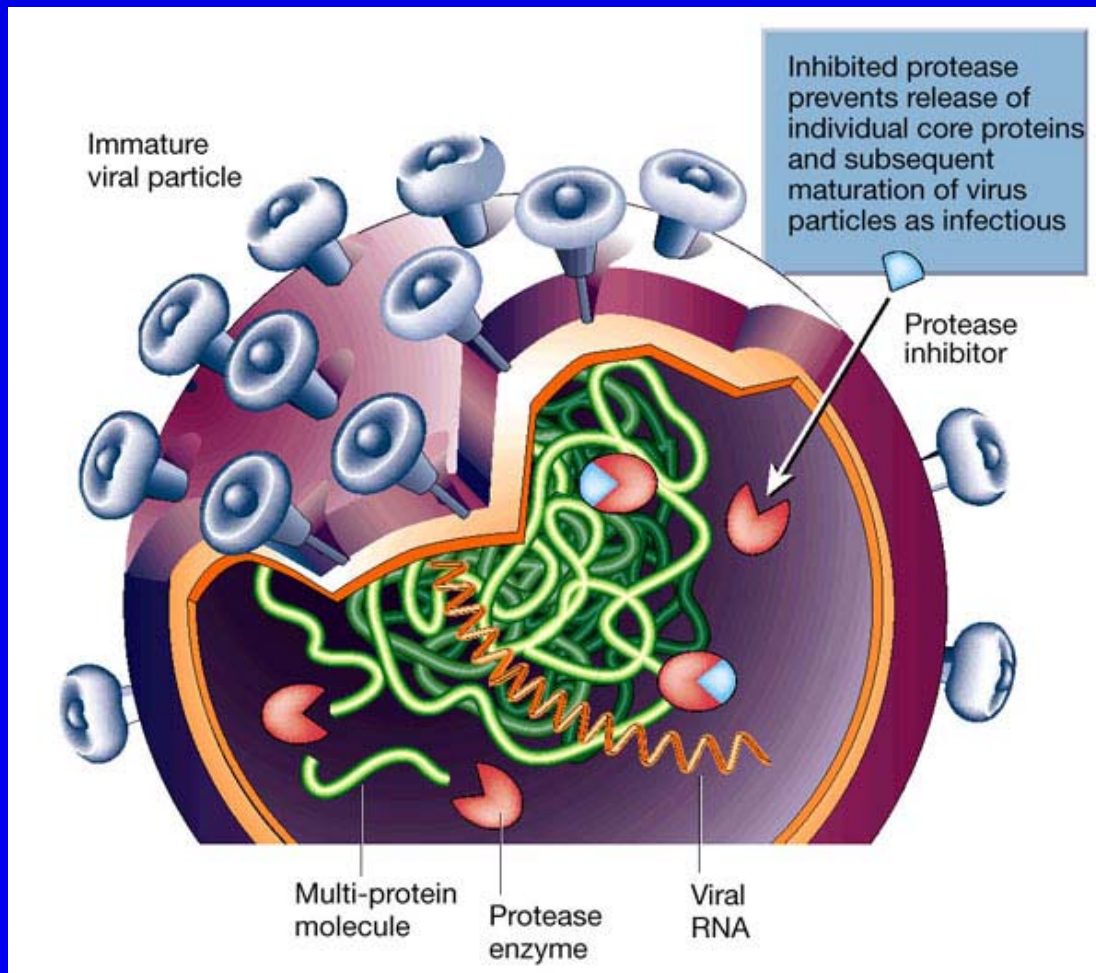
HIV Inhibitors



HIV-1 inhibitors

Protease inhibitors (PIs)

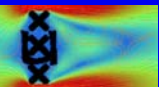
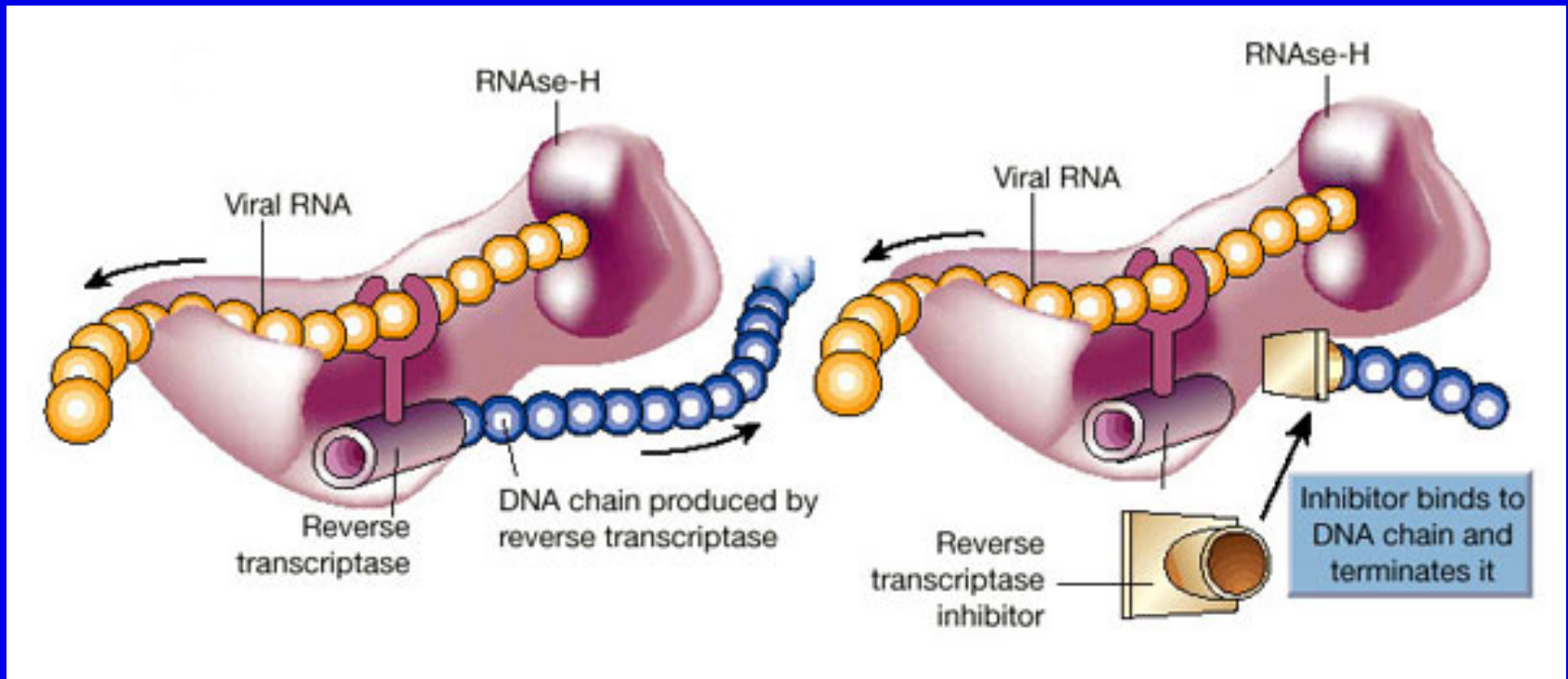
Saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and lopinavir/r



HIV-1 inhibitors

Nucleoside reverse transcriptase inhibitors
(NRTIs)

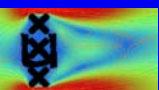
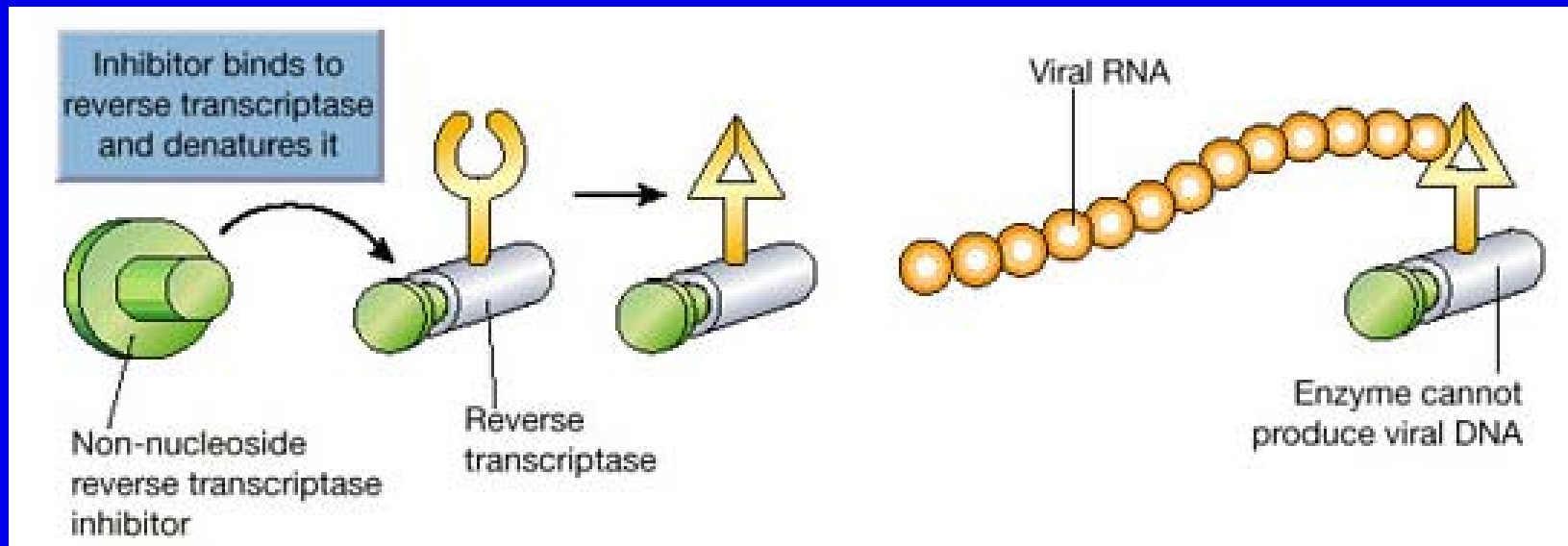
Zidovudine, didanosine, zalcitabine, stavudine, lamivudine and abacavir



HIV-1 inhibitors

Non-nucleoside reverse transcriptase inhibitors
(NNRTIs)

Nevirapine, delavirdine and efavirenz

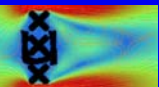


Resistance !

250000 HIV individuals in the USA and Europe with drug resistant viruses.

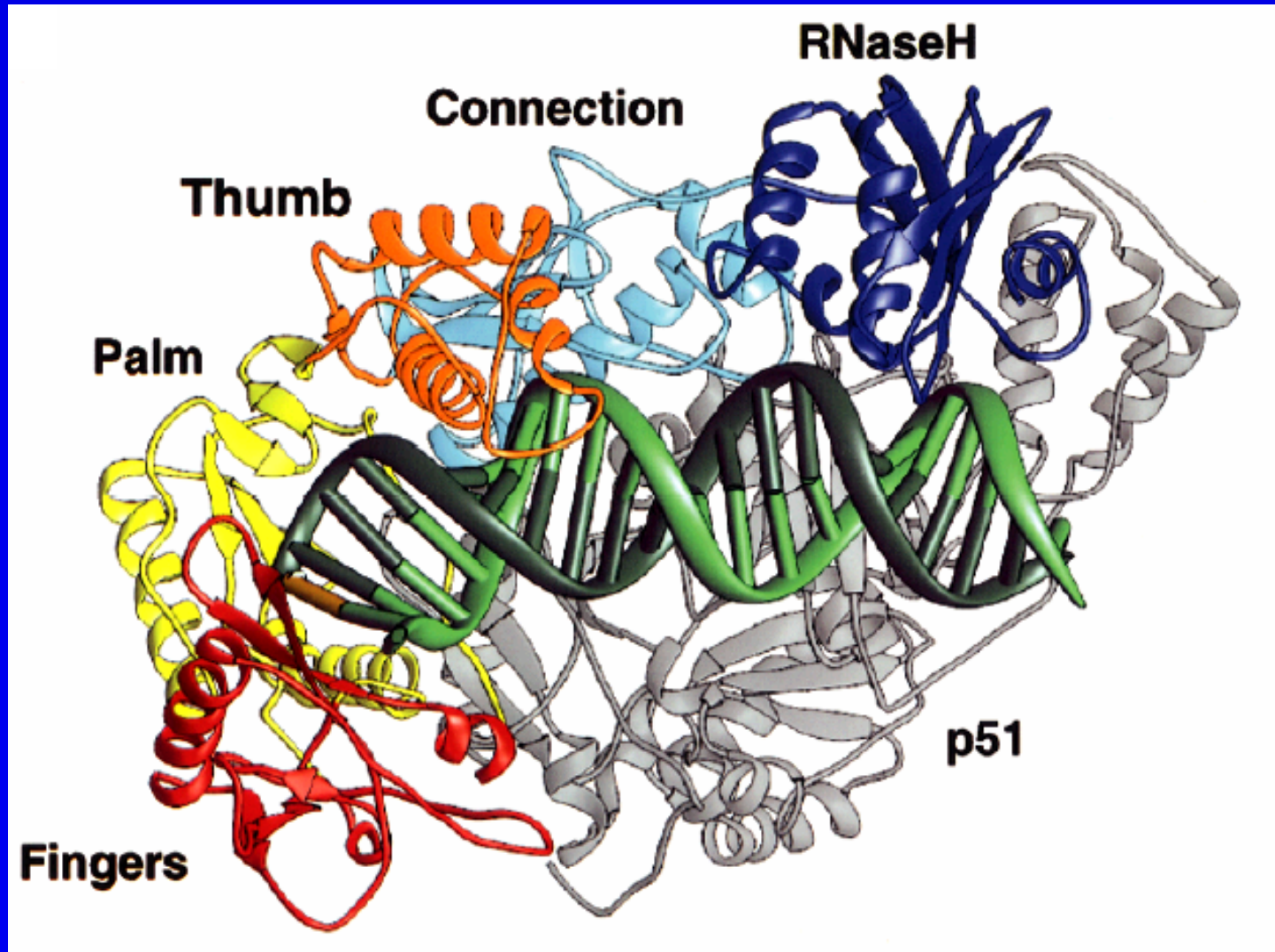
10% of new infections in USA/Europe occurs with viruses that have at least one drug resistant mutation.

Small proportion of patients die because we have no drugs to inhibit their viruses

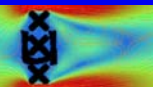
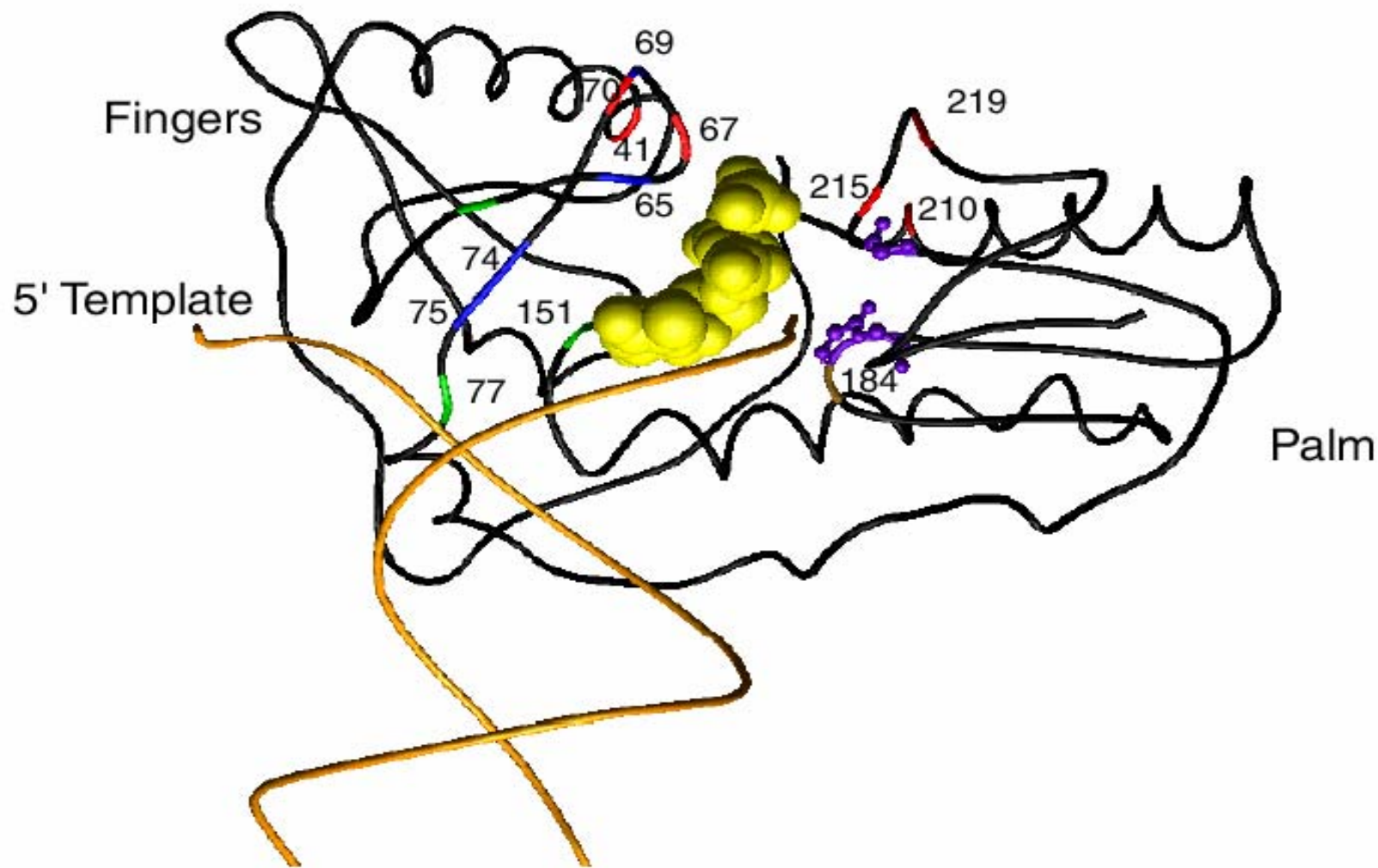


Virology of HIV-1

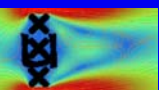
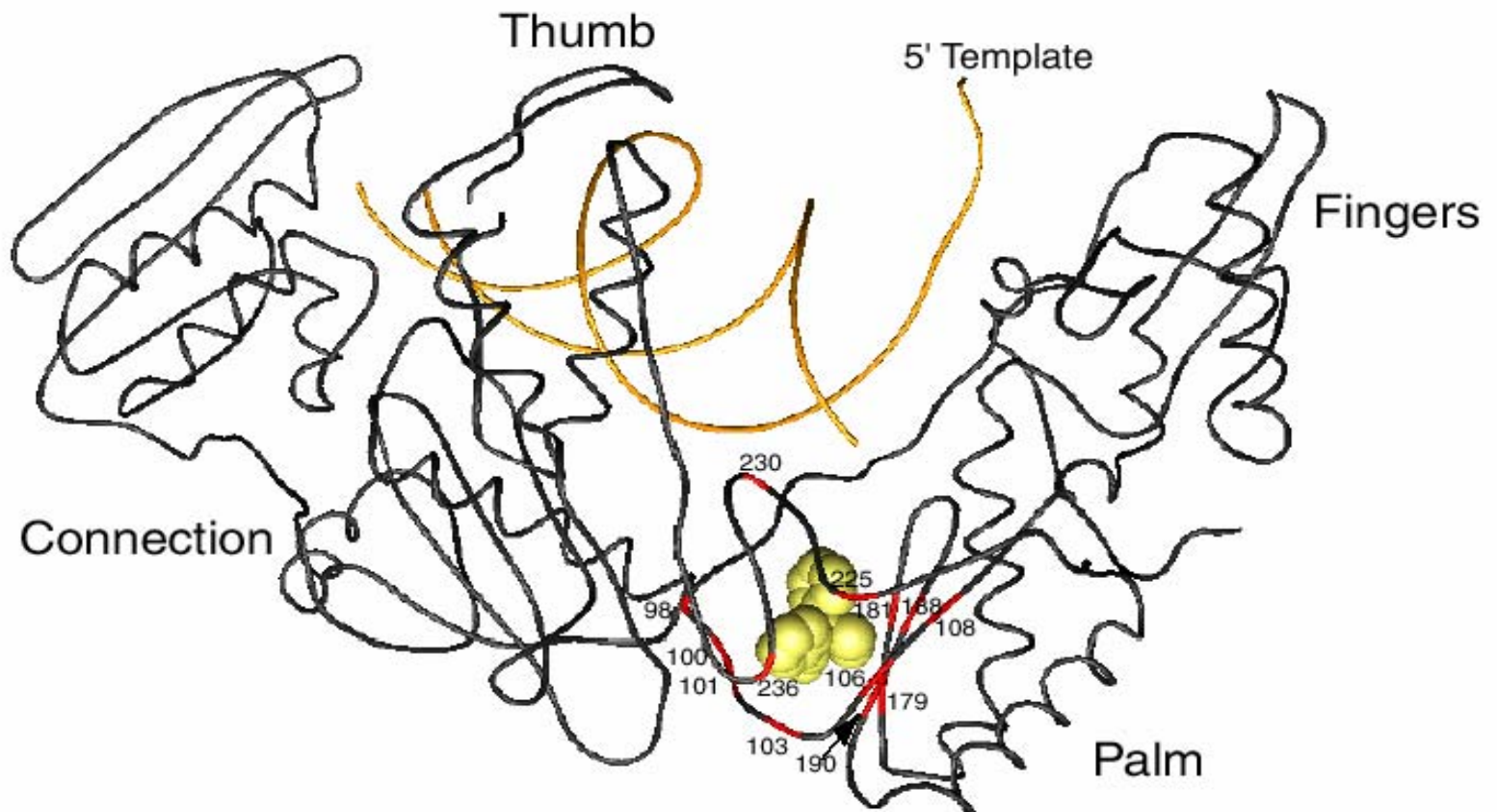
Reverse transcriptase (RT)



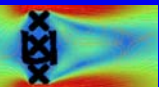
NRTI resistance mutations



NNRTI resistance mutations

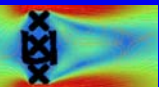


Accumulation of high level resistance

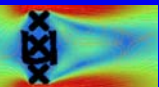
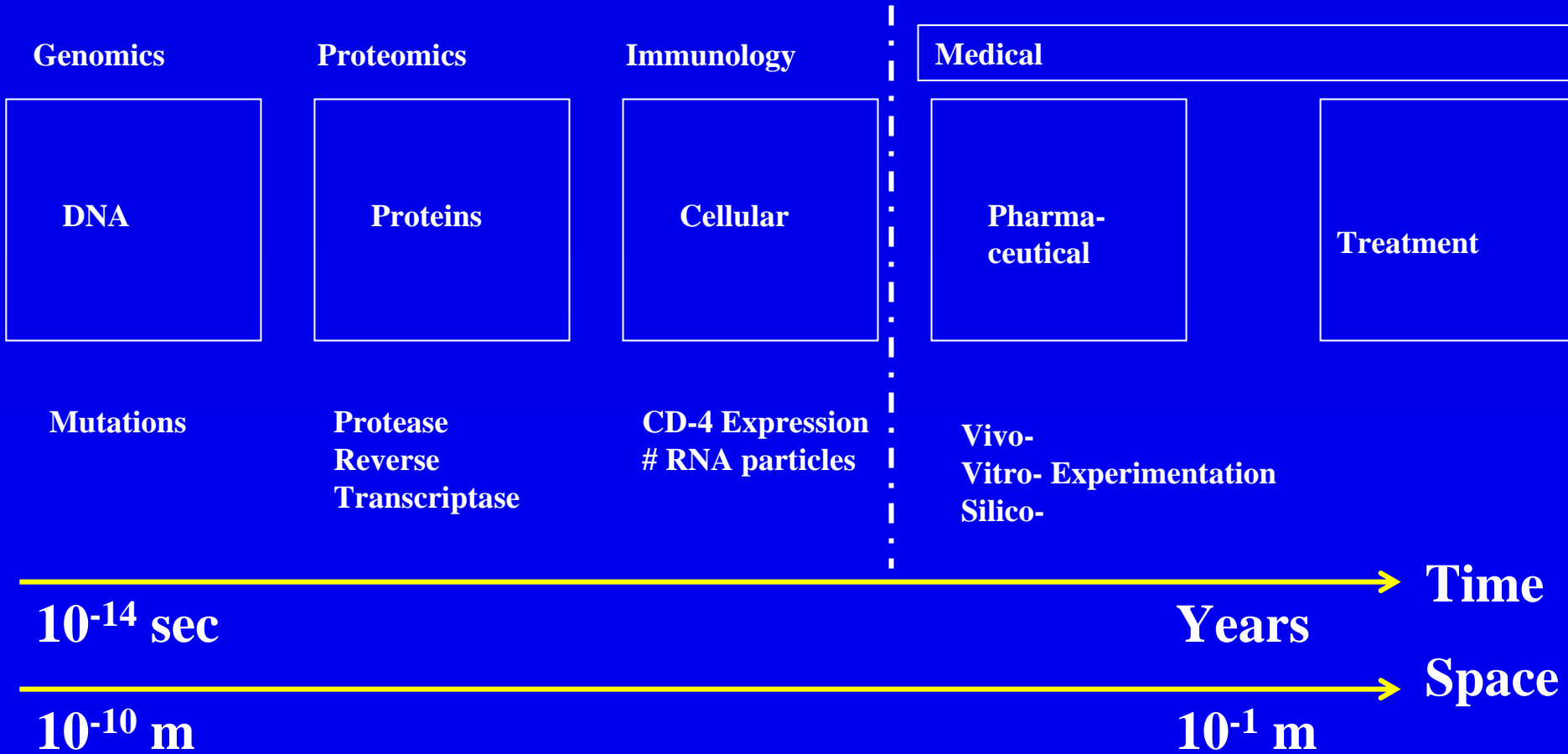


Our Approach

- No free ride: just incredibly difficult with combinatorial explosion
- Need *all scales all disciplines all data*
- From molecule to man to mankind
- *Combine disciplines, scales and information into one environment for decision support*



From Molecule to Man...



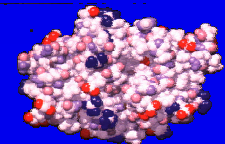
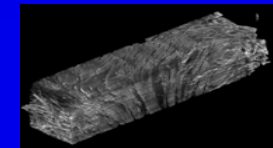
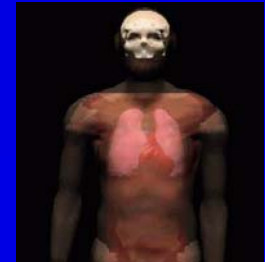
In silico humans-spatial & temporal scales

- 1 m person
- 1 mm electrical length scale of cardiac tissue
- 1 μm cardiac sarcomere spacing
- 1 nm pore diameter in a membrane protein

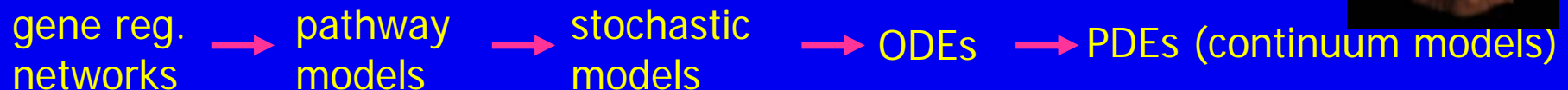
Range = 10^9

- 10^9 s (70 yrs) human lifetime
- 10^6 s (10 days) protein turnover
- 10^3 s (1 hour) digest food
- 1 s heart beat
- 1 ms ion channel HH gating
- 1 μs Brownian motion

Range = 10^{15}

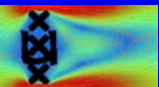


Requires a hierarchy of inter-related models



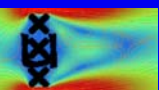
Our Approach...

- Mine literature (vivo & vitro)
- Derive rules (semantics and logic)
- Find patterns (Biostatistics)
- Simulate drug-protein complexes (MD: Physics)
- Simulate Immune response (CA: Immunology)
- Analyze temporal behavior (data mining)
- Analyze population trends (CA & graph theory & CN)
- Derive rules for Decision Support (CS, Logic)
- Provide integrated environment (Virtual Lab)



What we need

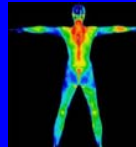
- High Performance Computing ← Mesoscopic Simulation
- High Throughput Computing ← Parameter Space Exploration
- Data Disclosure ← Dbase Federation and Integration
- Data Fusion ← Parameter Transfer
- Access ← Visualization/VR & Roaming and Remote & PDA
- Secure Sharing ← Virtual Organizations



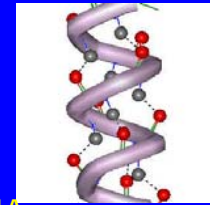
Intervention Parameters

drug dosage
drug level

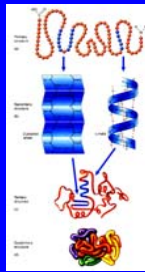
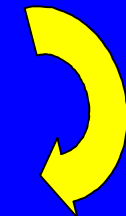
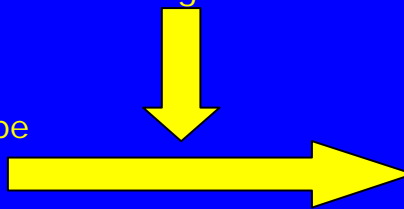
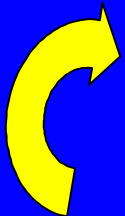
Primary Parameters



phenotype



RNA
(CD4)



protein
structure

*From molecule to man:
hierarchical data flow
model
for infectious diseases*

viral
fitness

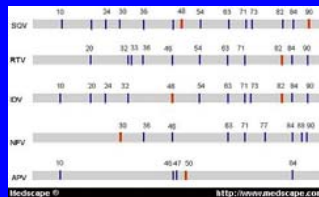


meta
parameter
virological

Micro Parameters



protease
mutations

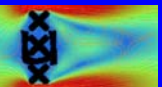
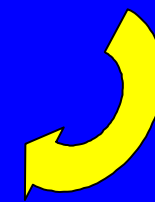


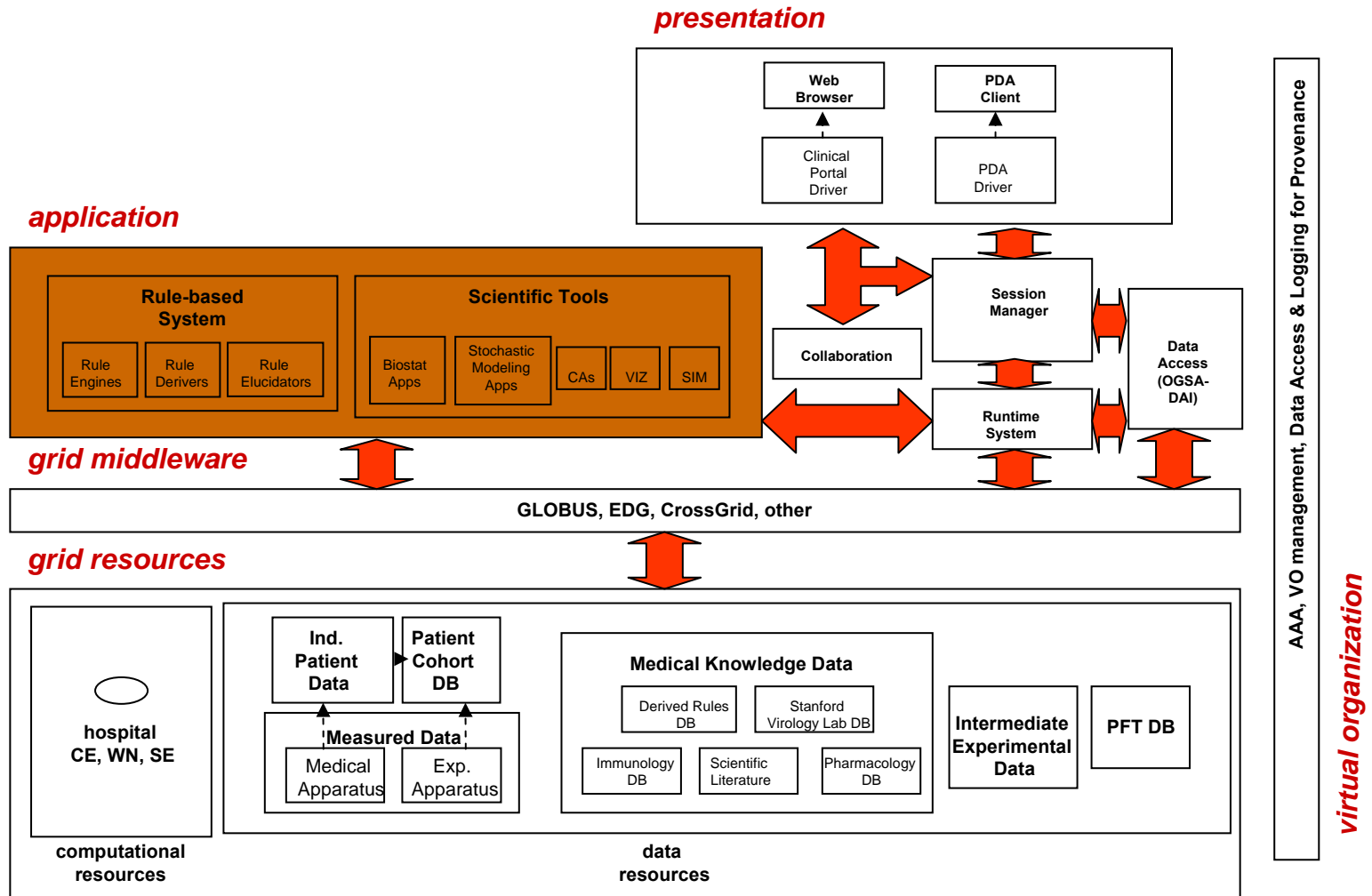
Clinical:
-weight
- opportunistic
infections
and tumors
-survival



meta
parameter
clinical

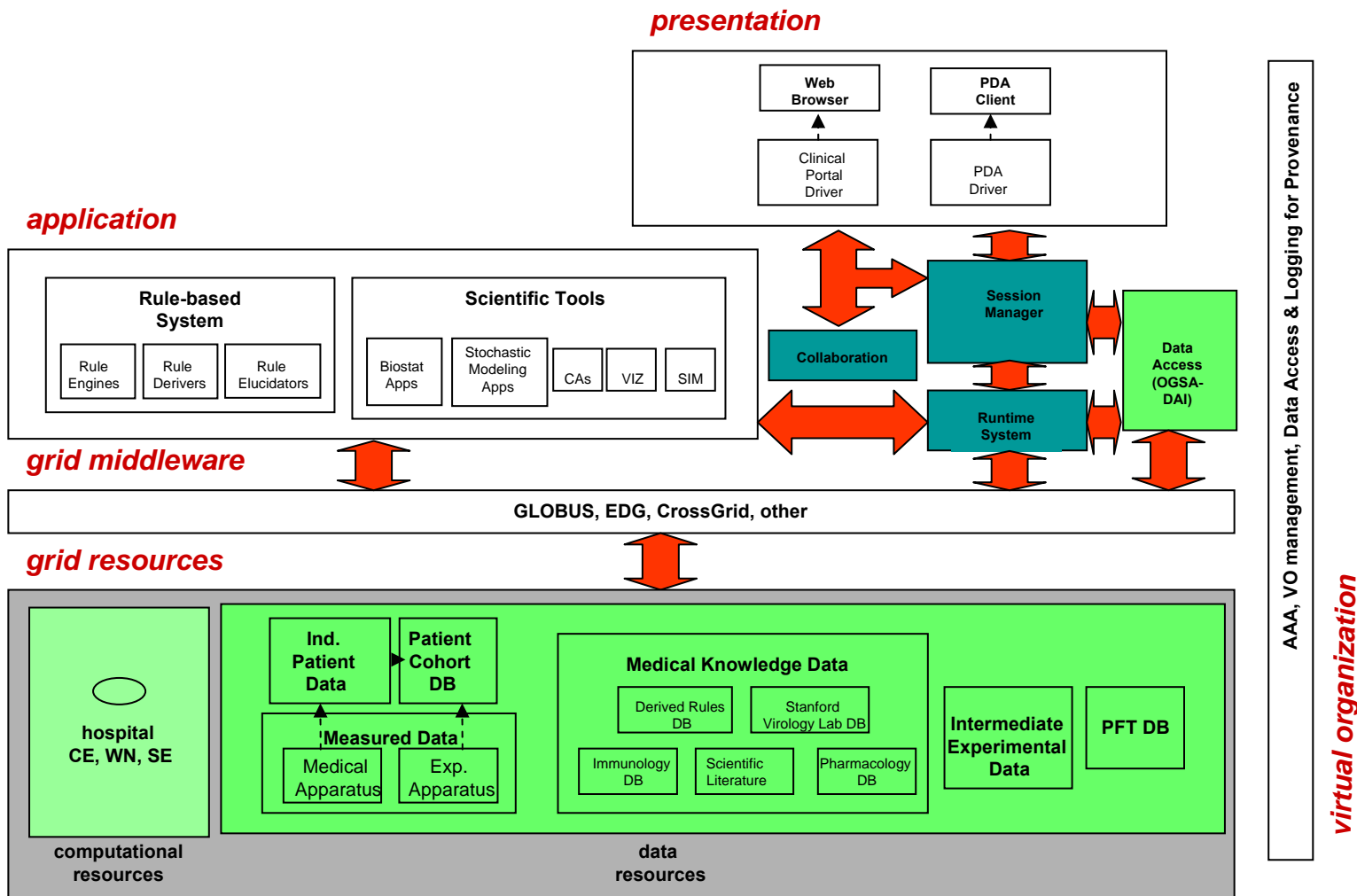
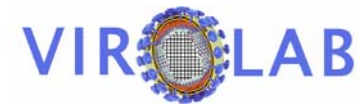
Macro Parameters





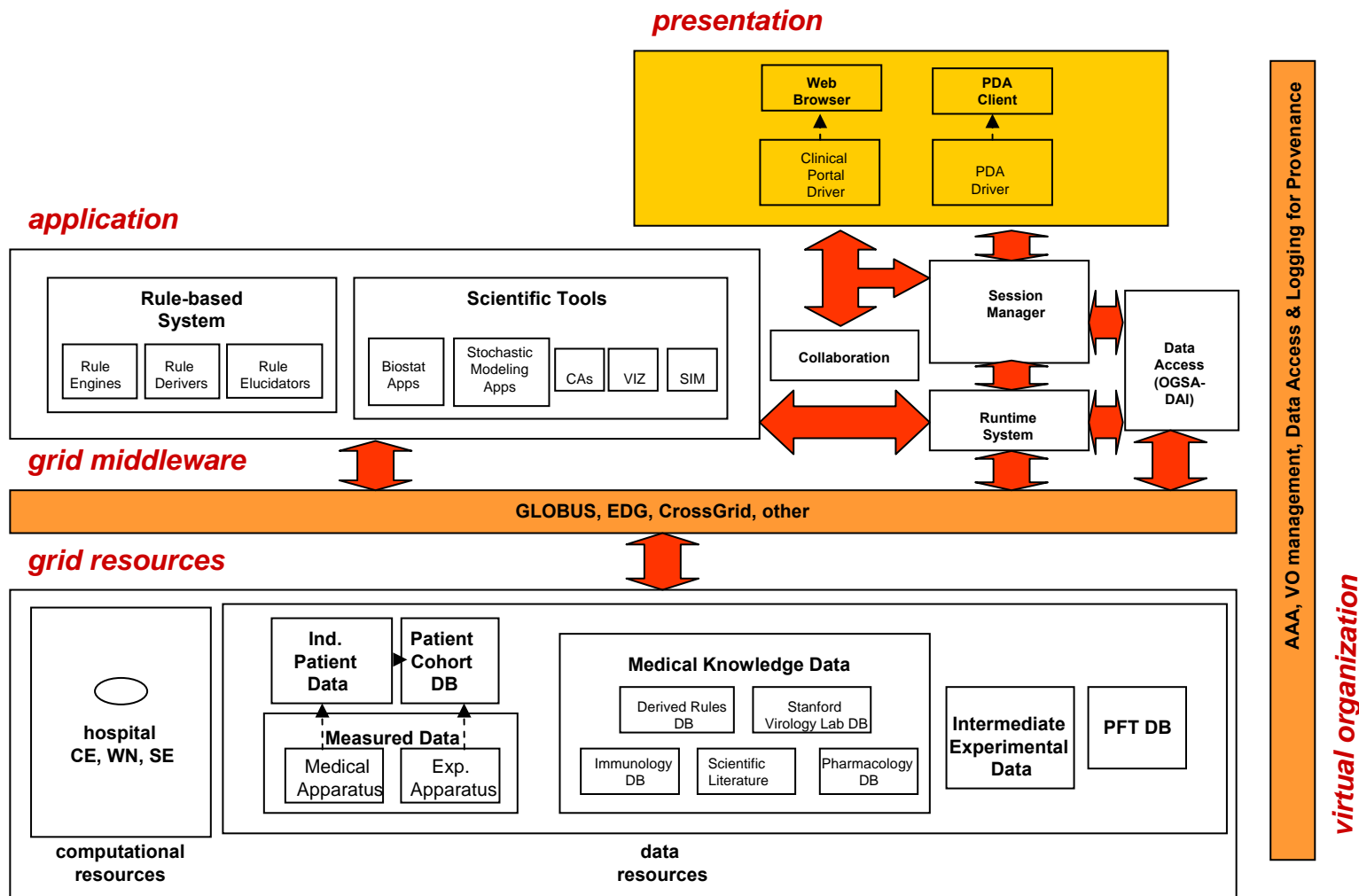
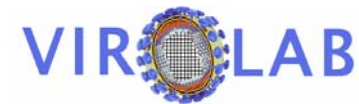


Data Perspective



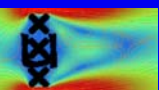


Grid Perspective



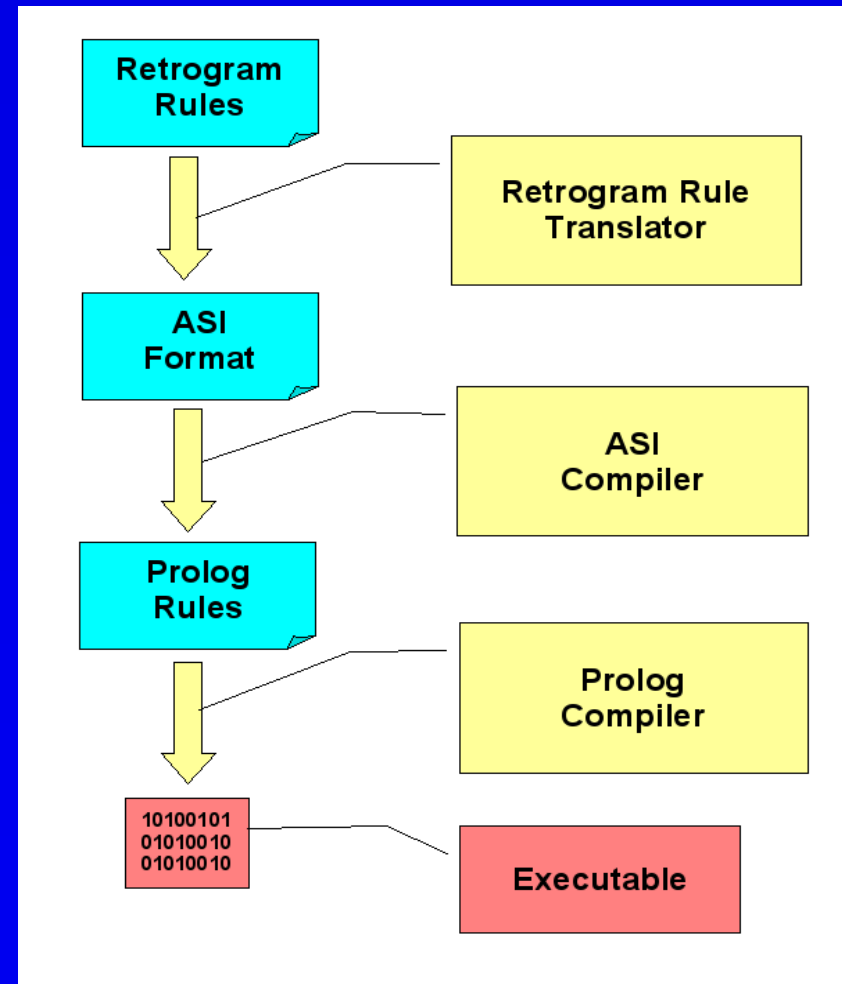
→ Integrated Decision Support

1. Text mining → Automatic Rule Generation
2. Molecular Simulation → Binding Affinities
3. Dynamics → Simulation of Immune System
4. Biostatistics → Patterns
5. Epidemiology → Complex Networks



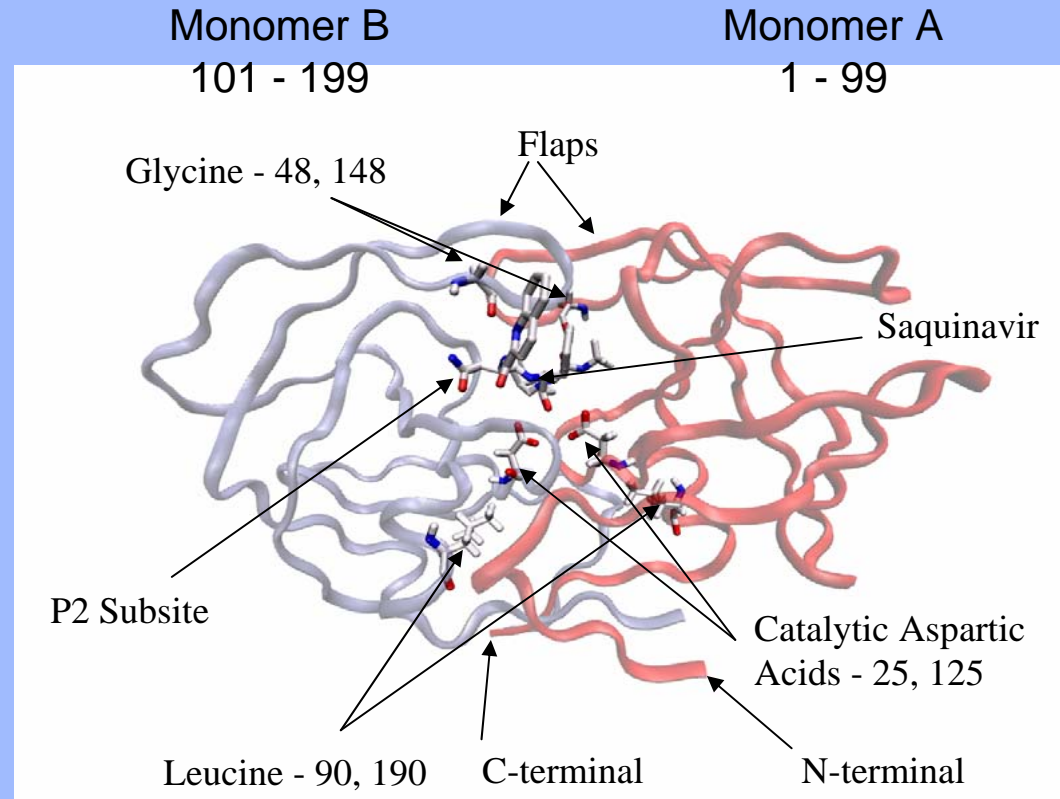
Building the rules

- Deconstruct & reconstruct RetroGram rule system
- Leverage Stanford HIVdb ASI rule format
- Prolog suitable target language: rule-based
- Portable solution
- Process existing rulesets in ASI format (Stanford HIVdb, Rega, ANRS, etc.)
- Machine Learning through provenance tracking

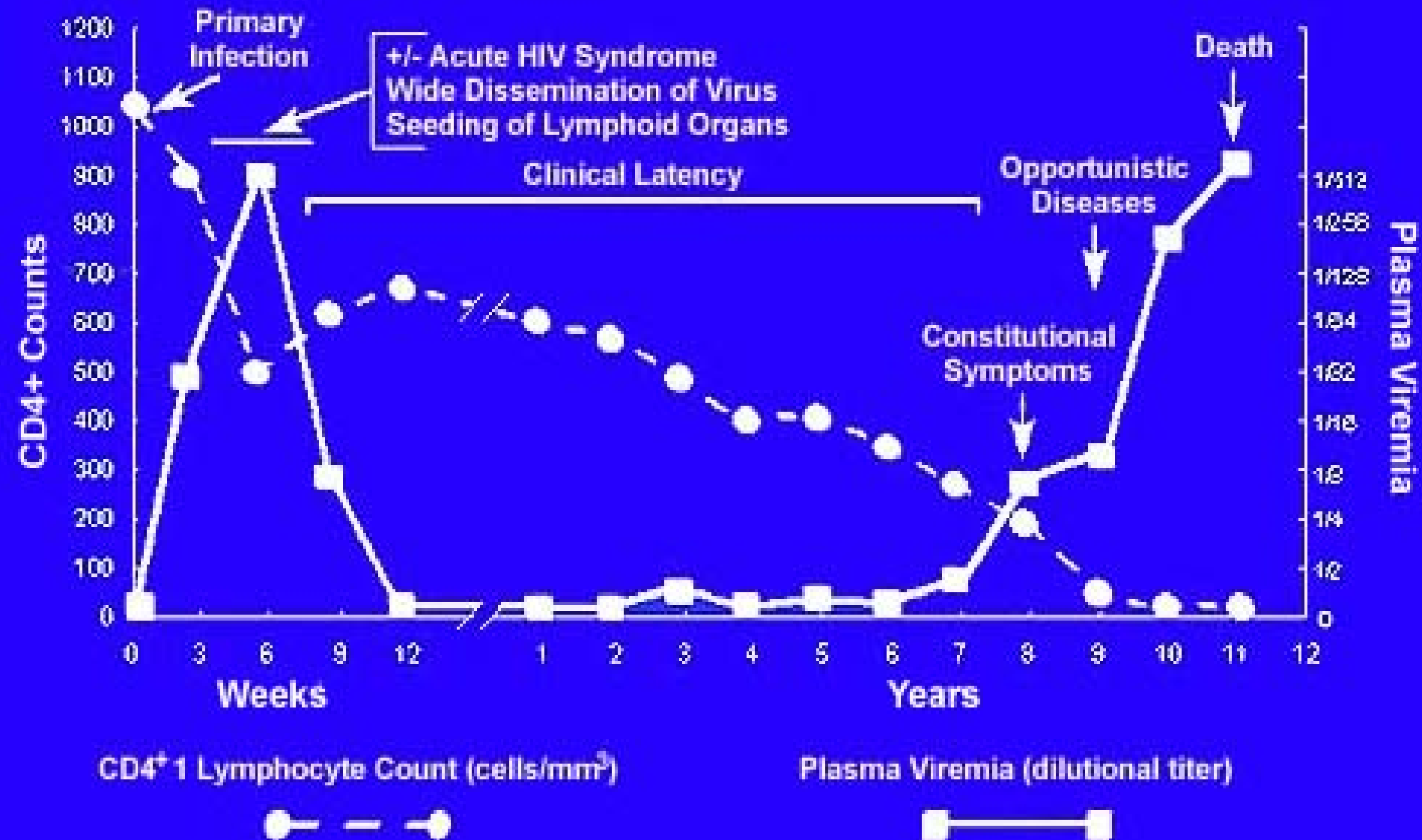


Molecular Dynamics of Drug Binding

- Use Molecular Dynamics Simulations to compute trajectories
- 4 main binding affinity methods:
 - Linear Integration Energies (LIE)
 - Molecular Mechanics, Poisson Boltzmann, Surface Area (MMPBSA)
 - Thermodynamic Integration (TI)
 - Free Energy Perturbation (FEP)

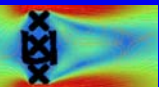


Infection Dynamics



Dynamics: Modelling Intra Host

- Two ways to model: mathematical (PDE/ODE) and cellular automata models
- The main advantage of cellular automata with massive parallelism, locality of cellular interactions and simplicity of cells is to emphasize the emergence and the importance of spatial structure
- Up to now, no reports to model the therapy of HIV infection using CA



Computational Model Part II

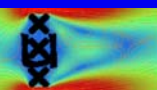
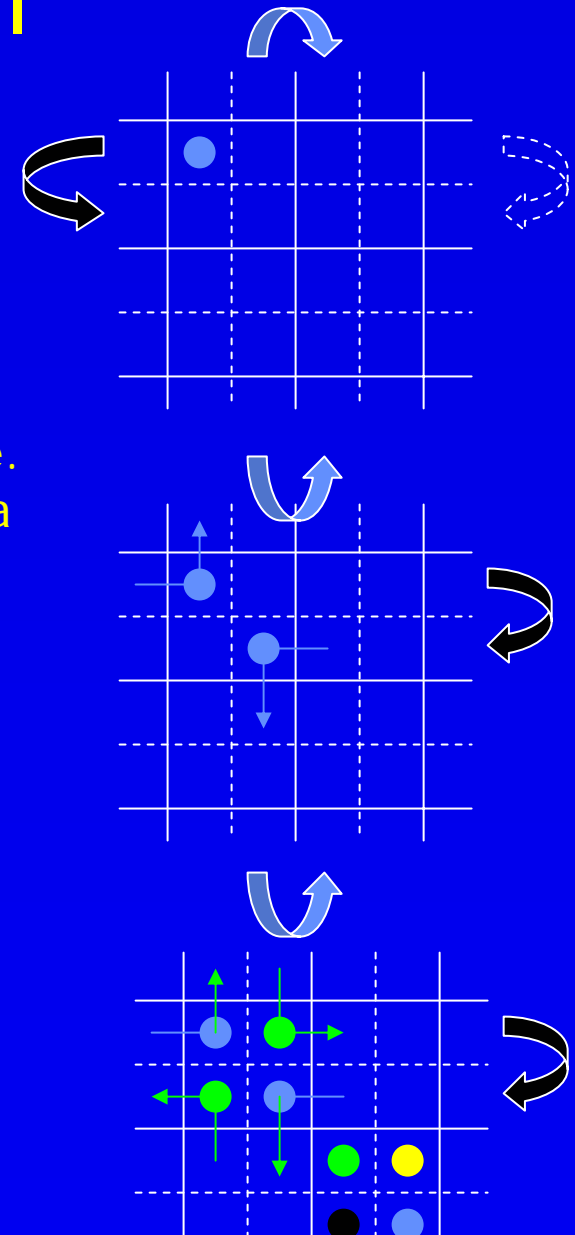
■ HI Model with Lymphocytes Mobility

- Margolus neighbors (2 X 2 block rule).
- **2D-Brownian Movement**
(1) rotate the block's contents one-quarter turns clockwise or rotate it counterclockwise.
(2) decision will depend on the outcome of a coin toss

- **Modified TM-GAS rule**

TM-GAS IF CENTER COLLISION
 ELSE PHASE {CCW CW}
 THEN > PLNO

Modified TM-GAS
 IF DEAD CELL COLLISION
 ELSE PHASE {CCW CW}
 THEN > PLNO



Computational Model Drug effects

■ Drug Therapy of HIV Infection Model

Rule 1:

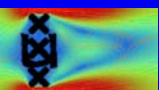
(a) If there is one A1 neighbor after the starting of drug therapy, N ($0 \leq N \leq 7$) neighbor healthy cells become infected-A1 in *the next time steps* with probability p_{resp} . Otherwise, all of eight neighbors become infected-A1.

N represents effectiveness of drugs.

$N = 0$: no replication; $N = 7$: less effective for the drug.

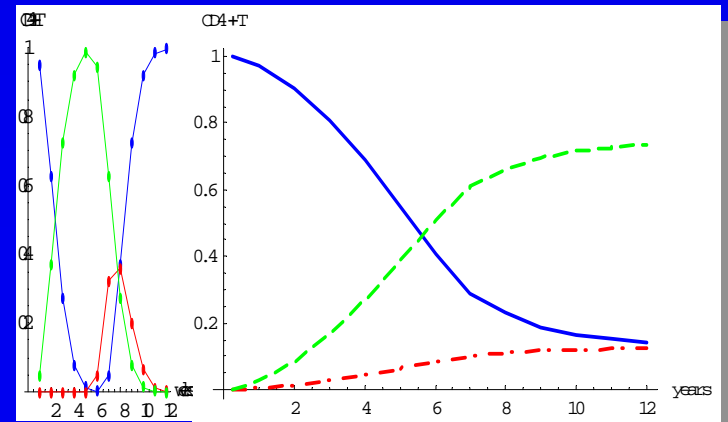
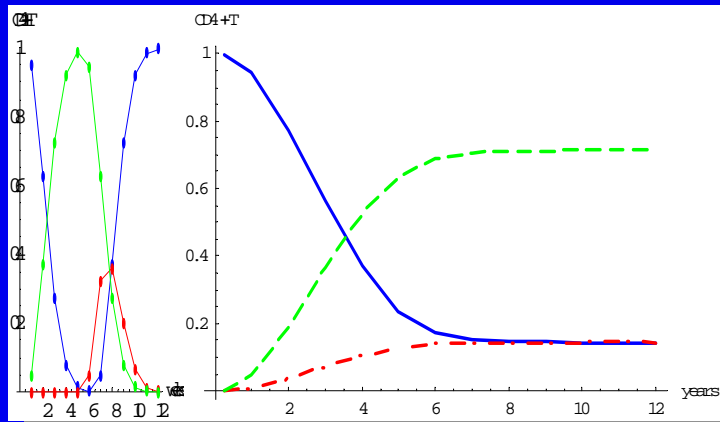
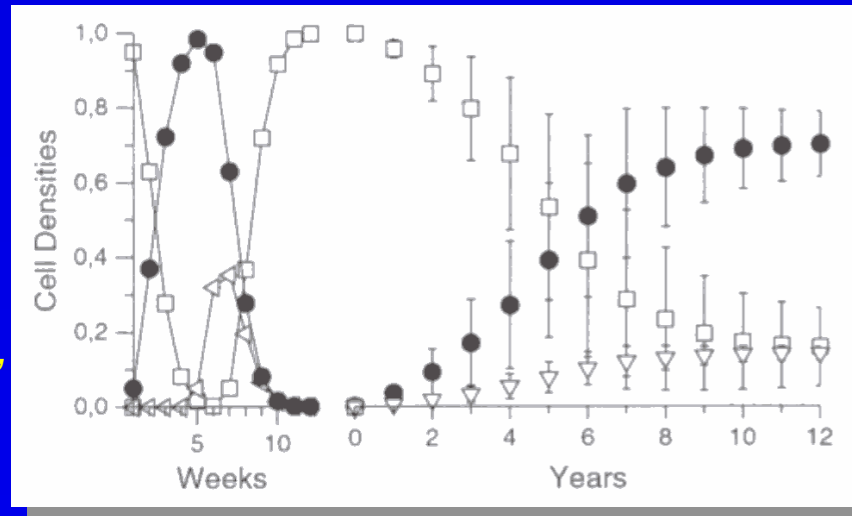
$p_{resp}(t-t_s)$ represents certain response function of drug effects over the time steps (t). The t_s is the starting of treatment.

The other rules stay the same for Basic DTHI
Advanced DTHI (add other rules)



Simulation Results: Validation of Dynamics

*P.M.A. Sloot et al.,
LNCS 2002*

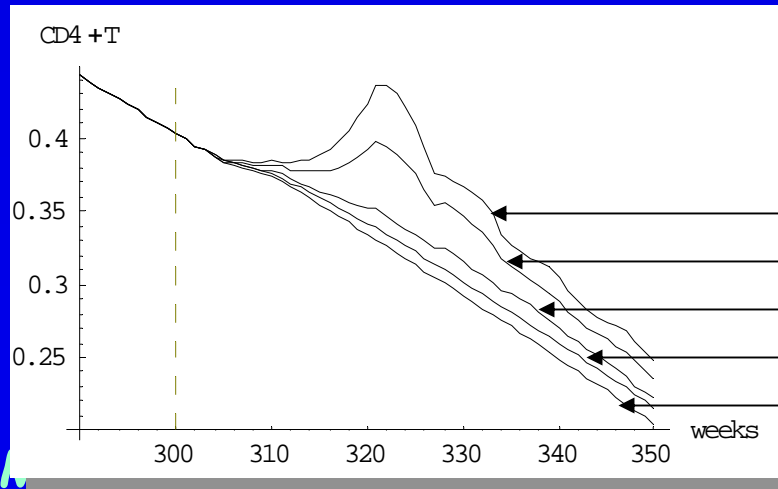


Healthy Infected Dead

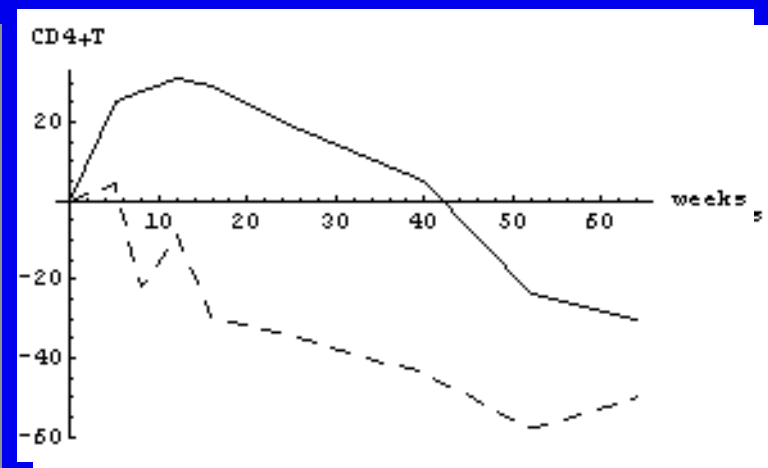
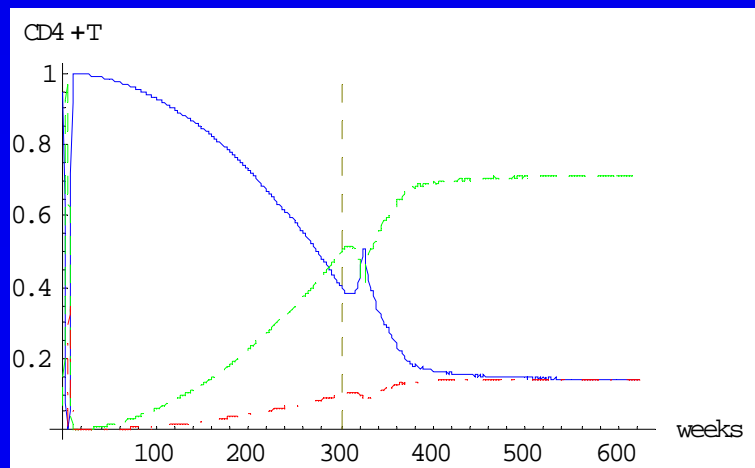
Simulation Result: Drug Response



Different Drug Effectiveness

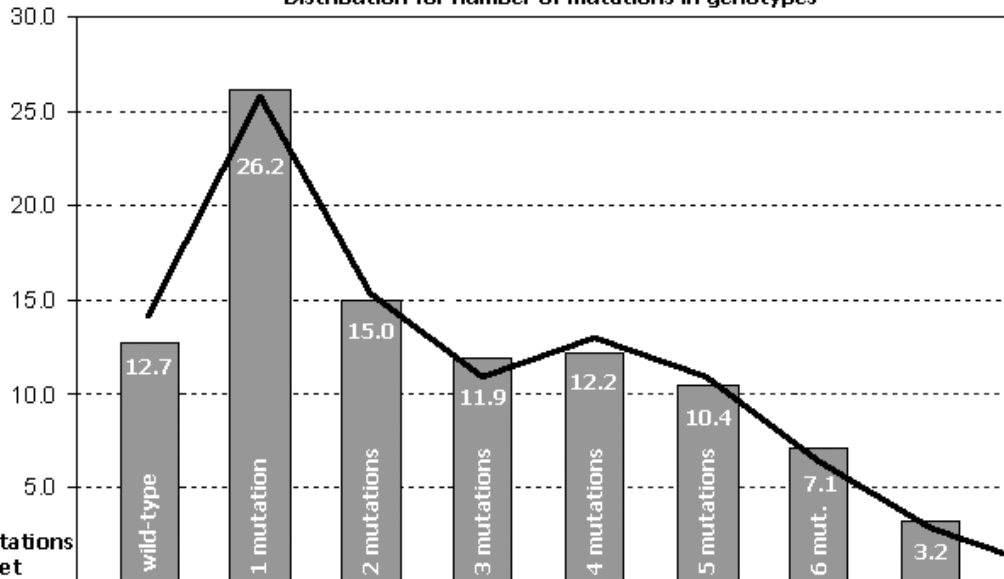


$N = 0$
 $N = 1$
 $N = 4$
 $N = 7$
No treatment

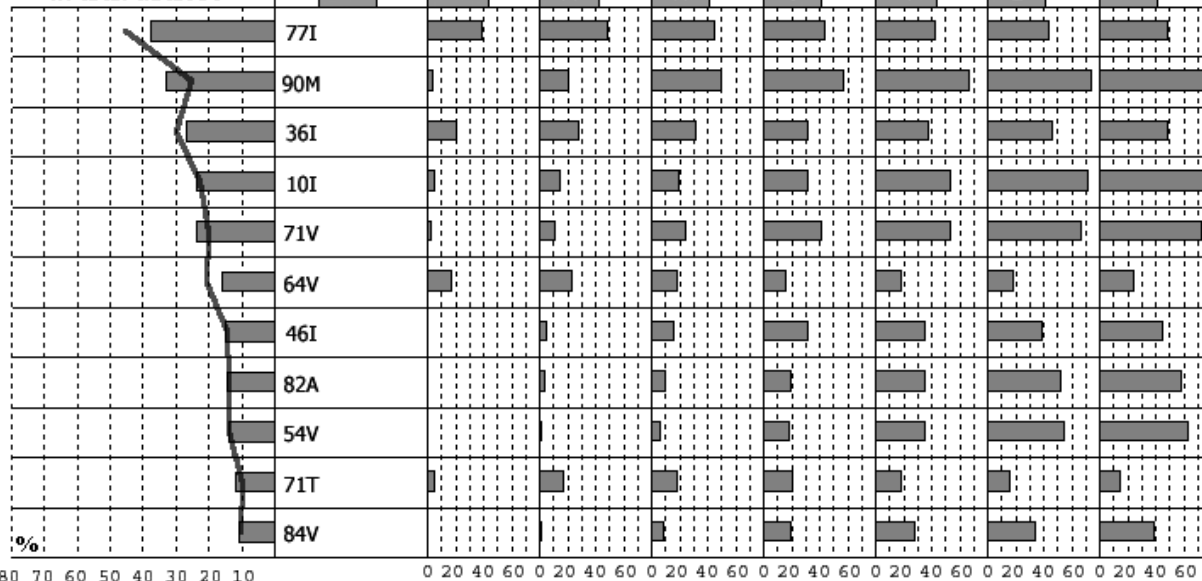


Population Level Biostatistics ...

Distribution for number of mutations in genotypes



Distribution of mutations in total dataset



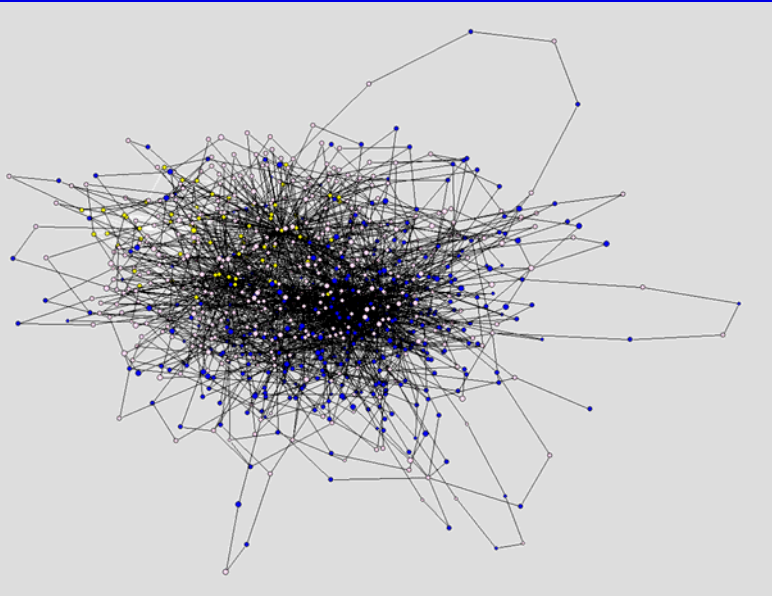
'Blurred' Dbases: Monte Carlo Simulation of

USA: 43620 patients; examined from August 9, 1998 to May 5, 2001

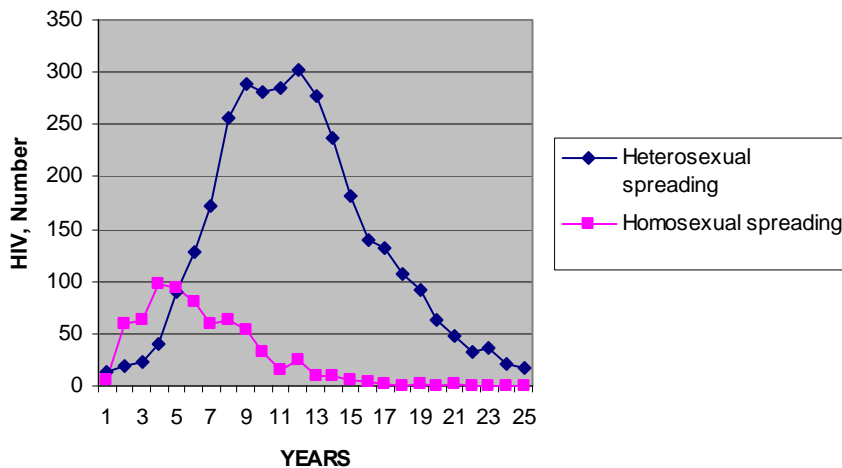
Two distinct mutations in Protease: Treated and Untreated secondary Infections.

P.M.A. Sloot et al.,
Journal of Clinical Monitoring and Computing, vol. 19, nr 4-5 2005.

HIV Population: Networks -1

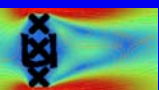


- Example of the bipartite network of sexual contacts with additional links of homosexual contacts. Blue nodes are men, pink nodes are women, and yellow nodes homosexual men.

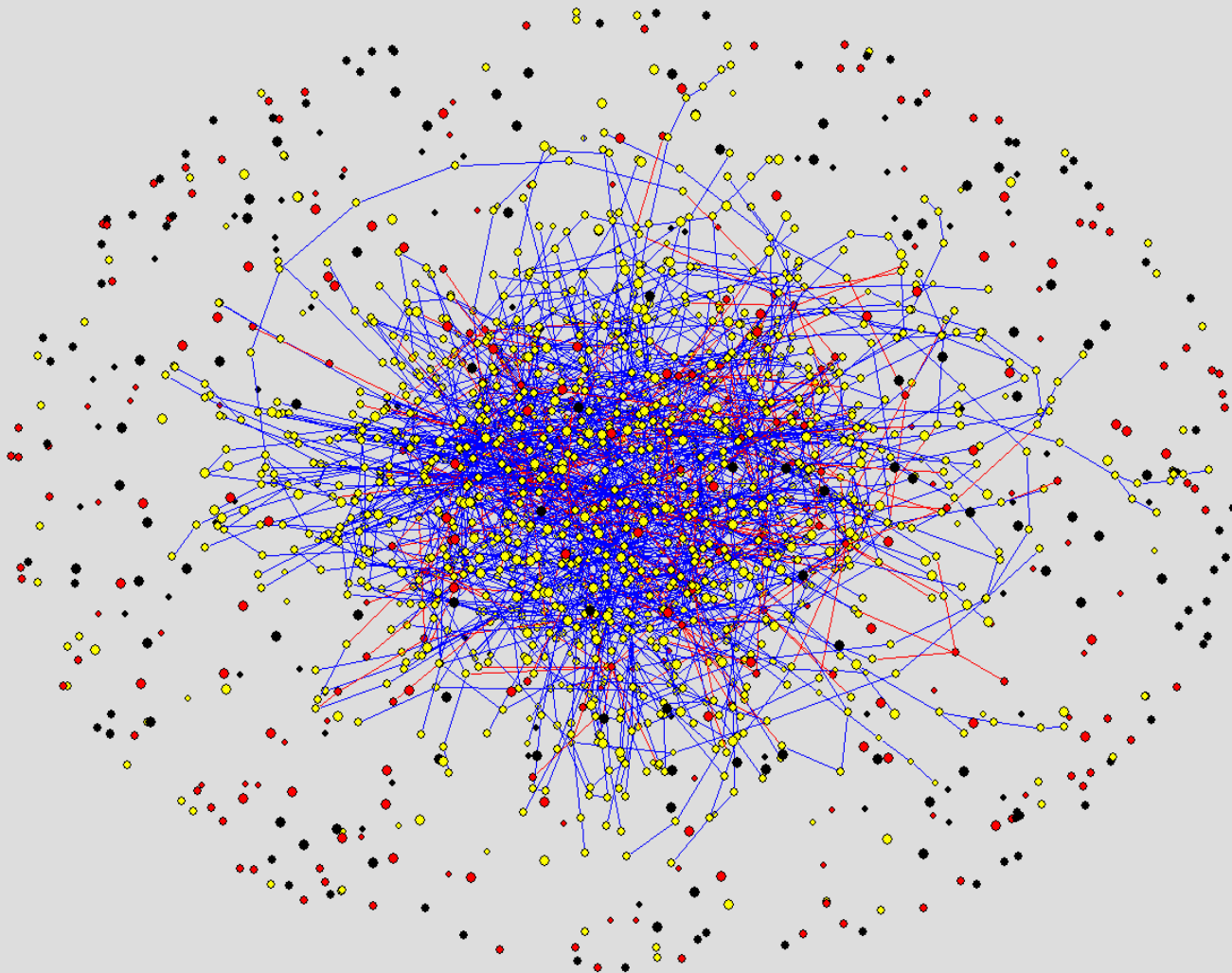


- HIV modeling with separation of spreading type.

(data source: UNAIDS/04.16E (June 2004))



HIV Population: Networks -2



HIV dynamics
simulation:
Initial network
configuration to
Final
configuration
(5 years of
simulation)

Yellow nodes
healthy
individuals,
Red infected
Black dead

Resulting DSS version 1.0

RetroGram 1.4

Patient ID:

RetroGram 1.4

Patient Details

Laboratory Information

HIV Therapy
Decision Support
Interpret Substitutions

Help

Exit

Protease Substitutions

Reverse Transcriptase Substitutions

Relevant

71T, 63H, 82T, 30N

Relevant

41L, 67N, 69D, 75I, 103N, 184V, 215Y

Natural

16E, 39S, 57R, 62V, 72V

Natural

211K, 20R, 90I, 102K, 121H, 122E,
142V, 162Y, 177E, 203D

Unreported

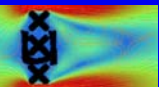
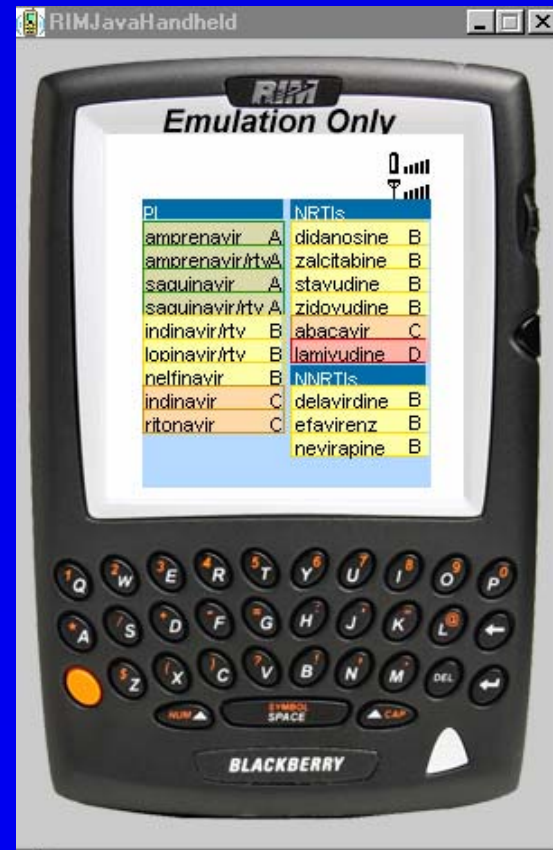
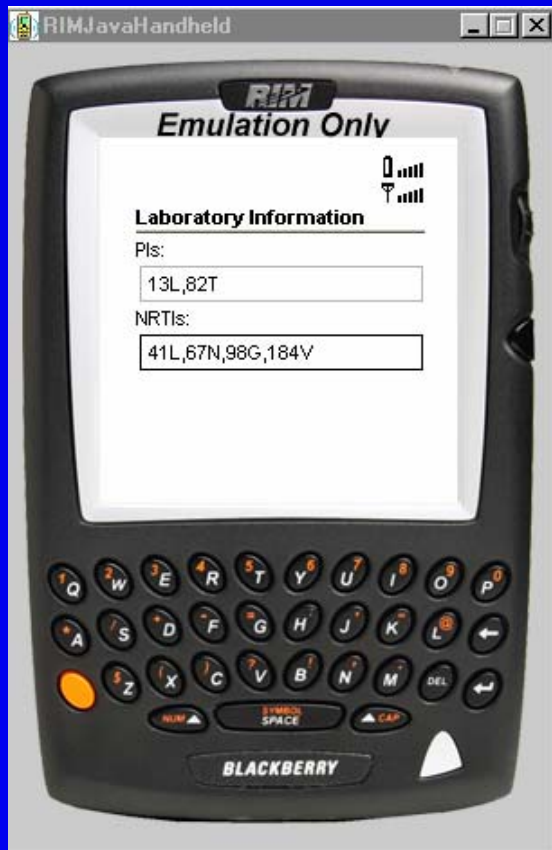
None

Unreported

31L, 35M, 162D, 277K, 286A

Back

Remote access



Ranking quality

Table 3. Association of baseline genotypic susceptibility score (GSS) with change from baseline human immunodeficiency virus (HIV) RNA levels (multiple linear regression).

System ^a	HIV RNA level change per unit increase in GSS, log ₁₀ copies/mL			
	At 3 months		At 6 months	
	Mean (95% CI)	P	Mean (95% CI)	P
Stanford hivdb	-0.14 (-0.33 to +0.05)	.14	-0.19 (-0.38 to -0.01)	.04
ANRS AC11	-0.16 (-0.34 to +0.01)	.07	-0.12 (-0.32 to +0.03)	.14
Rega 4.0	-0.12 (-0.32 to +0.08)	.25	-0.10 (-0.31 to +0.09)	.31
GuideLines 3.0	-0.21 (-0.40 to -0.02)	.03	-0.23 (-0.42 to -0.05)	.01
Retrogram 1.4	-0.18 (-0.41 to +0.04)	.10	-0.22 (-0.49 to -0.05)	.04
RCG	-0.10 (-0.28 to +0.08)	.29	-0.16 (-0.34 to +0.02)	.08
HIVresistanceWeb	-0.18 (-0.39 to +0.02)	.07	-0.23 (-0.43 to -0.03)	.02
Menéndez-Arias	-0.15 (-0.34 to +0.03)	.10	-0.11 (-0.29 to +0.07)	.24
CHL 3.2	-0.21 (-0.40 to -0.02)	.03	-0.12 (-0.30 to +0.06)	.20
Detroit Medical Center	-0.01 (-0.19 to +0.17)	.91	-0.01 (-0.19 to +0.17)	.90
São Paulo University	-0.11 (-0.27 to +0.05)	.19	-0.17 (-0.33 to -0.01)	.03

De Luca, *Journal of infectious diseases* 2003

Results: Interpretation tools CD4

System ^a	CD4 ⁺ cell count change from baseline per unit increase in GSS, cells/ μ L			
	At 3 months		At 6 months	
	Mean (95% CI)	P	Mean (95% CI)	P
→ Stanford hivdb	+2 (-15 to +19)	.82	+23 (+3 to +43)	.02
→ ANRS AC11	+13 (-1 to +28)	.08	+17 (-1 to +34)	.06
→ Rega 4.0	+15 (-1 to +31)	.07	+28 (+9 to +48)	.004
→ GuideLines 3.0	+10 (-6 to +26)	.22	+27 (+8 to +46)	.005
→ Retrogram 1.4	+24 (+5 to +42)	.01	+40 (+18 to +62)	<.001
→ RCG	+5 (-14 to +24)	.59	+19 (-3 to +42)	.09
→ HIVresistanceWeb	+21 (+2 to +40)	.03	+25 (+2 to +48)	.03
→ Menéndez-Arias	+12 (-6 to +30)	.20	+15 (-7 to +37)	.18
→ CHL 3.2	+15 (-2 to +32)	.07	+21 (+2 to +42)	.03
→ Detroit Medical Center	+16 (0 to +33)	.05	+18 (-1 to +38)	.07
→ São Paulo University	+14 (-2 to +30)	.09	+25 (+6 to +44)	.01

De Luca, *Journal of infectious diseases* 2003

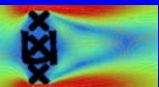
Conclusions

- System science: Not for the faint of heart
- Diminishing boundaries of classical sciences
- Whole is much more than the sum of the parts

- DSS: open research issue
- Grid technology is enabling system science
- Security is open issue

- Virolab: promising ranking results awaiting further evaluation

- Simulations become more and more complex and realistic

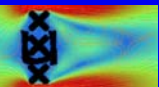


Outlook: The Future of Simulations:

*'How long before the simulators sit up,
swing their legs over the bedside and walk
up to you complaining of pain?'*

*In: From Dummies to Dollars, aka— "Holy Moly, How do I Make Money
off these Simulators?", Feb 2005*

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UCL: London: Peter Coveney et al.,

HLRS: Stuttgart: Stefan Wesner et al.,

ICLMI, Rome: Andrea de Luca

IRSICAIXA: Barcelona: Lidia Ruiz et al.,

SPstU: St. Petersburg: A.V. Bouchanovski et al.,

NTU: Singapore: Tai Joc Cing et al.,

GridWise: Krakow: Pawel Plaszczak et al.,

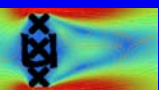
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'Retrogram' Trademark 713908, University of Amsterdam

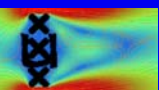


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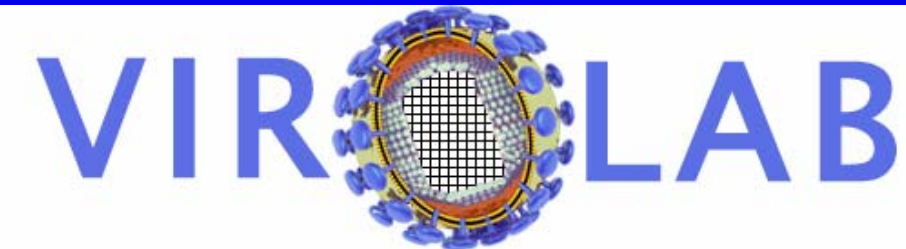
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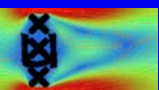
Support



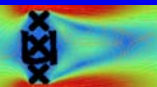
www.virolab.org



<http://www.vl-e.nl/>



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