Johns Hopkins Engineering

Immunoengineering

Immunoengineering: Modeling

HIV Drug Modeling

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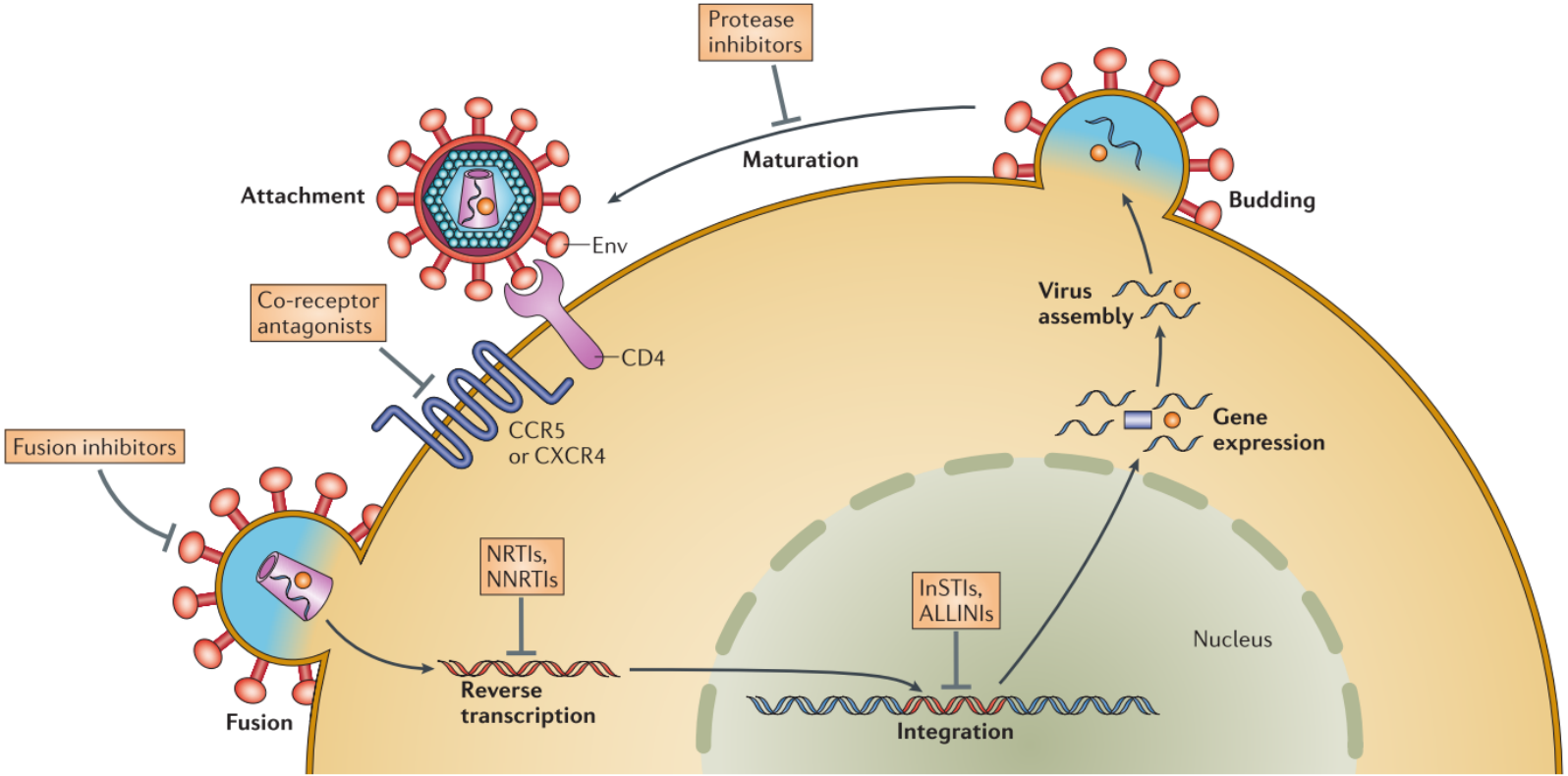
HIV Life Cycle



Laskey et al. “A mechanistic theory to explain the efficacy of antiretroviral therapy” *Nature Perspectives* 12, (2014): 772-780.

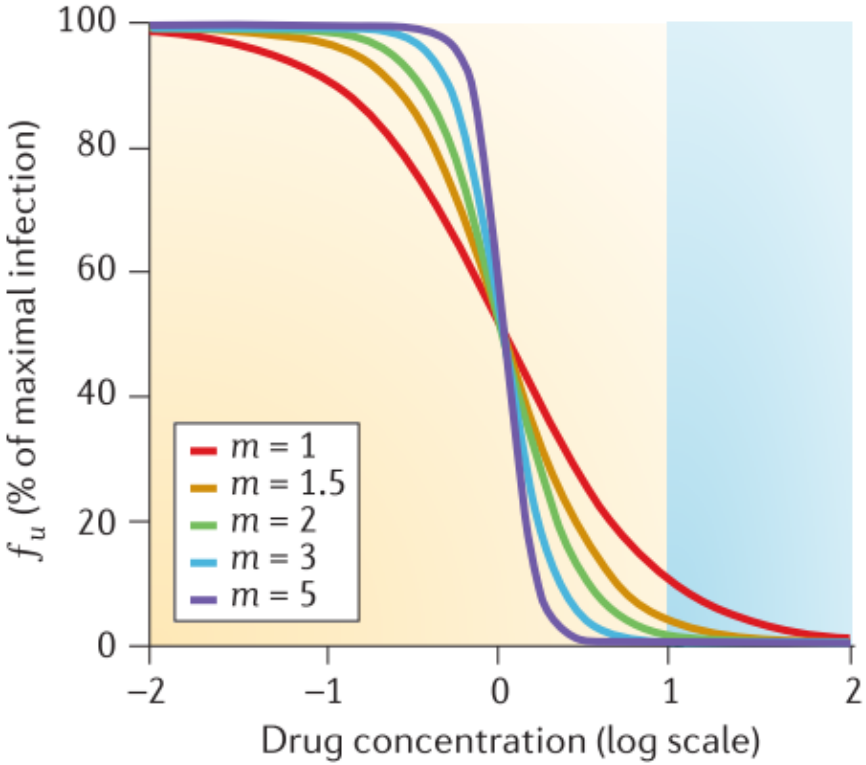
Anti-retroviral therapy (ART)

- Lifelong therapy, prevents infection of new target cells
- cART (combination ART) = combinations of many drugs against HIV
- Many combinations have not been tested
- Models of ART may quickly screen a large number/combination of drugs

cART Efficacy

- Dependent on 5 factors
  - Pharmacokinetics (concentration/time drug is in body)
  - **Pharmacodynamics** (antiviral activity at specific concentration)
  - **Additive, multiplicative, synergistic, or antagonistic interactions** between drugs
  - Patient adherence (major factor = pill burden/side effects)
  - Genetic barrier to evolution of drug resistance

Dose-response relationships are important when viral replication rate is very high



$$\frac{f_a}{f_u} = \left(\frac{D}{IC_{50}}\right)^m$$

f_a	fraction of infection events affected by drug
f_u	fraction of infection events not affected by drug
D	drug concentration
IC_{50}	drug concentration that achieves half maximal efficacy of that drug
m	analogous to Hill coefficient

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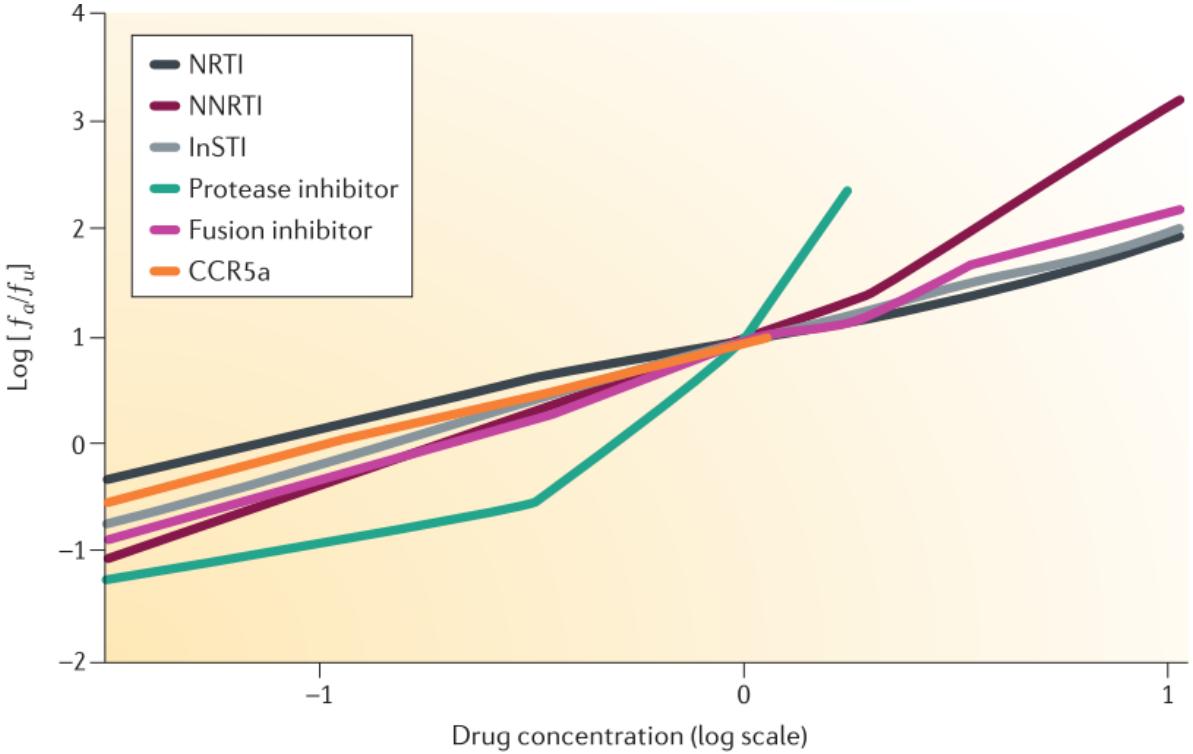
Dose response curves vary across ART drugs



- Slope of protease inhibitors and NNRTIs inflect upwards – non-constant *m*
- Higher effectiveness at higher concentrations → cooperativity

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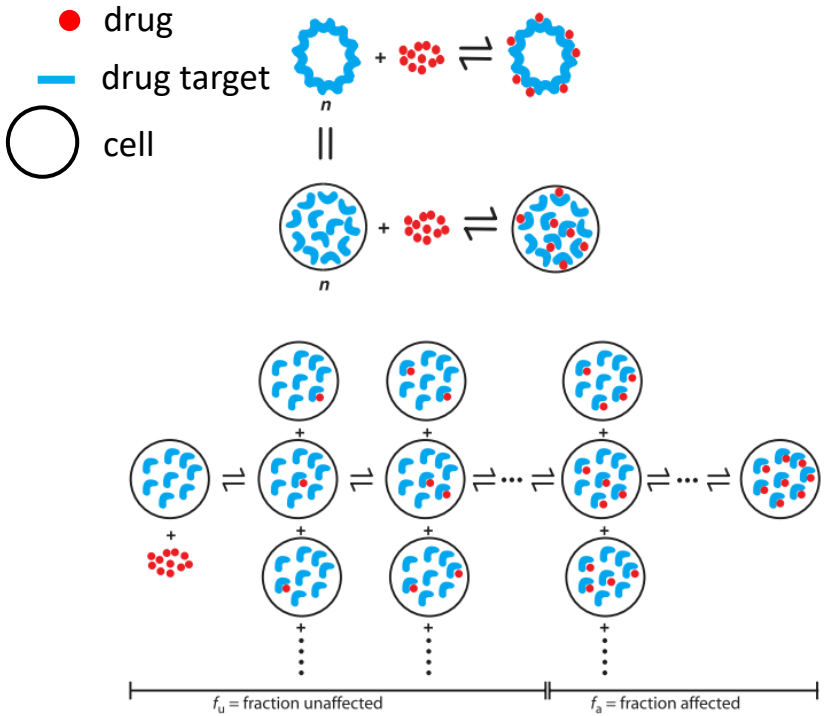
Cooperativity model: Critical subset model

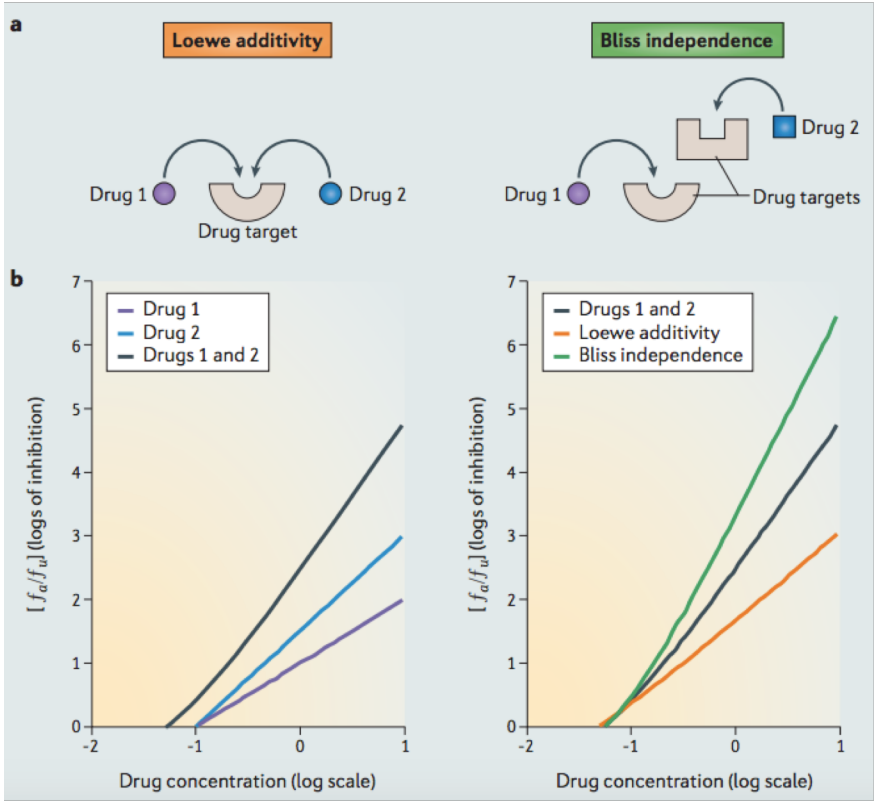
- Model explains how cooperativity is generated for anti-retroviral drugs with only one binding site on the target enzyme
  - Multiple copies of enzyme needed and enzyme critical to multiple parts of HIV life cycle
  - Pool of enzymes acts as a single “multivalent target”



Shen et al. “A Critical Subset Model Provides a Conceptual Basis for the High Antiviral Activity of Major HIV Drugs” *Science Translational Medicine* 3(91), (2011): 1-10.

Models describe drug interactions for cART

- Two theories to predict efficacy of drug combinations
  - Loewe additivity: drugs have shared MOA, compete for same binding site
  - Bliss independence: drugs function independently, have distinct targets; greater combined efficacy



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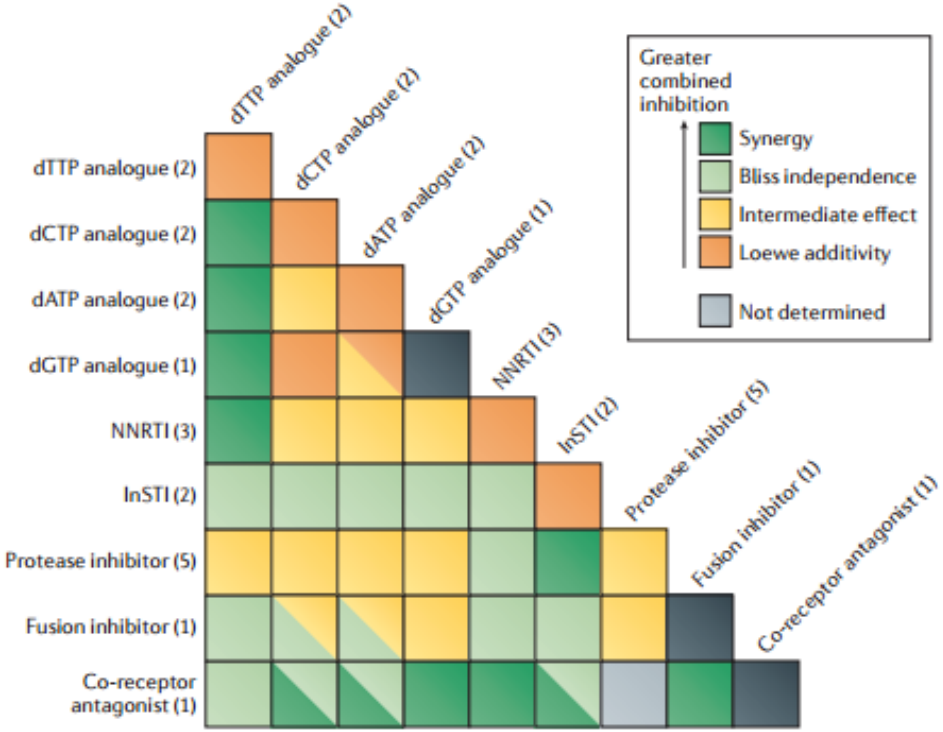
Predictions of interaction between drugs



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