The problem

- The emergence of drug resistance is one of the most prevalent reasons for HIV treatment failure

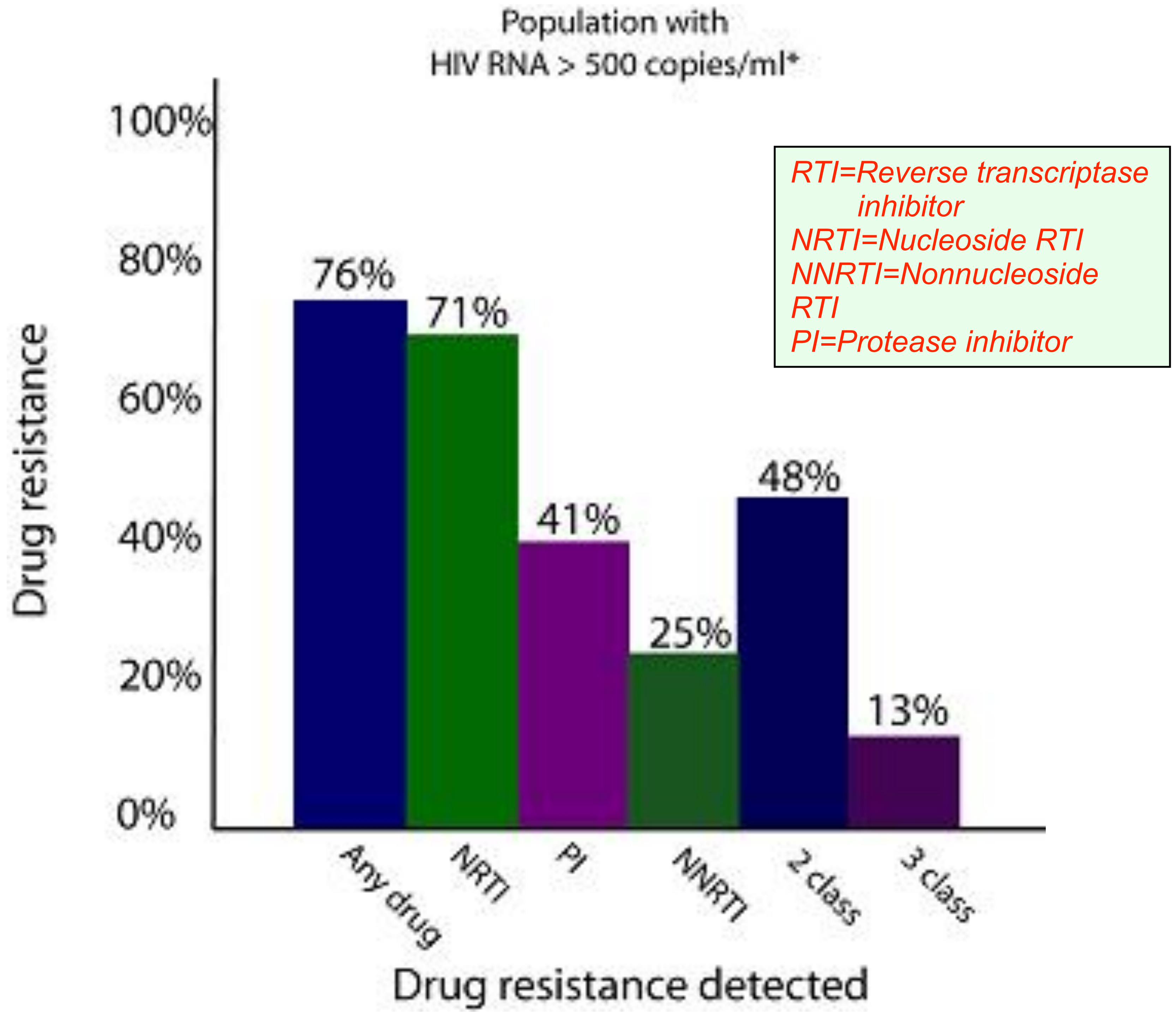
> "Clarification of the degree of adherence is the most urgent unanswered question in HIV research today"
> -The U.S. Department of Health and Human Services.

Research Questions

1. How can we quantify the relationship between drug levels and resistance?
2. Can we prescribe dosing intervals and dosages to prevent or reduce resistance?
3. For strongly adherent patients, how many doses can be missed before resistance emerges?

Outline

- Biology of HIV and drug resistance
- Mathematical model of resistance
- Impulsive differential equations
- Equilibria, periodic orbits, stability
- Quantify dosages and dosing intervals
- Derive adherence thresholds
- Extend results to combination therapy.


Population with
HIV RNA > 500 copies/ml*
Drug resistance
100%
80%
60%
40%
20%
0%
76%
71%
41%
25%
48%
13%
Any drug
NRTI
PI
NNRTI
2 class
3 class
Drug resistance detected
RTI=Reverse transcriptase inhibitor
NRTI=Nucleoside RTI
NNRTI=Nonnucleoside RTI
PI=Protease inhibitor

This is a timely question

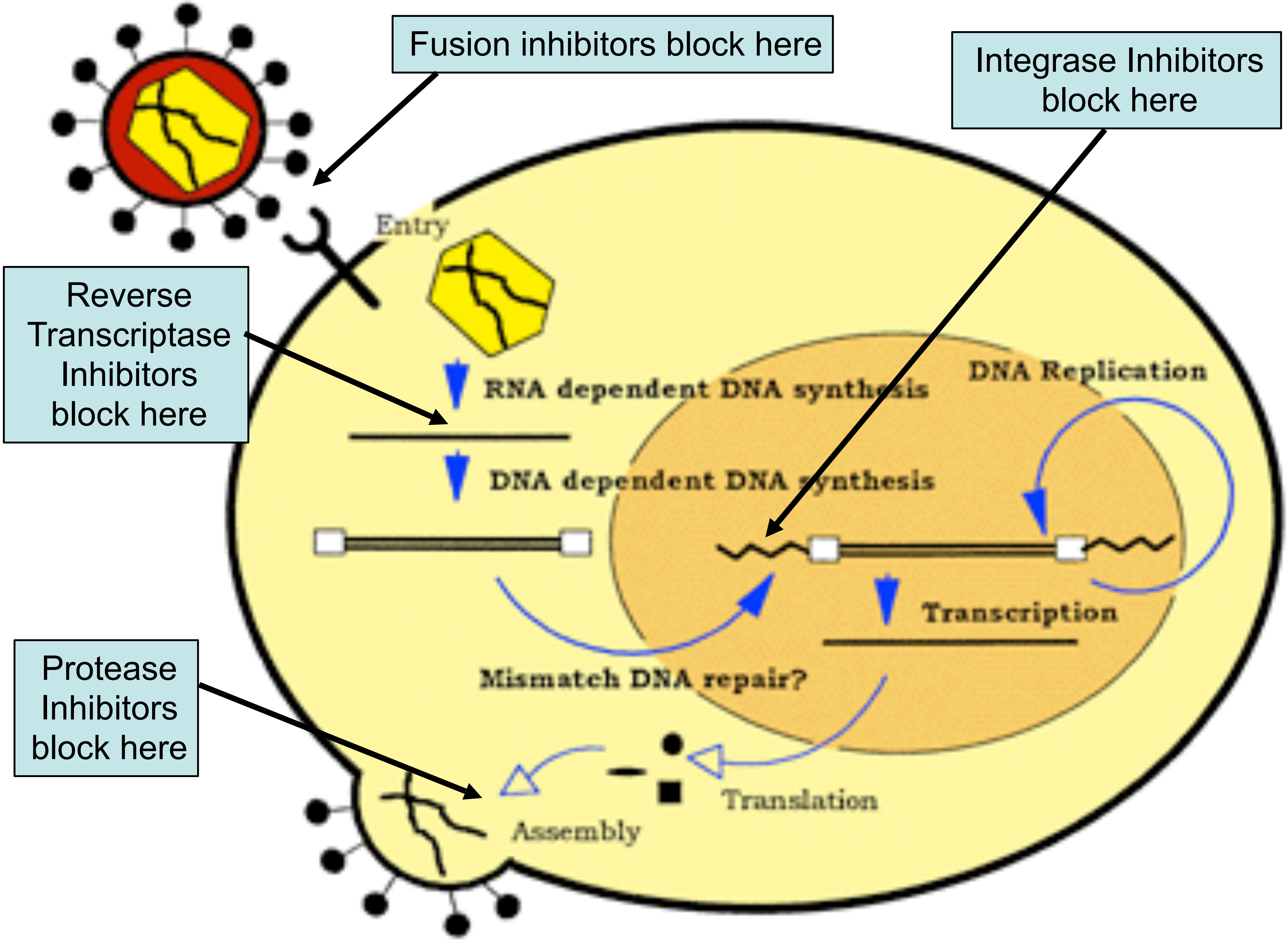
- Drug regimens to be introduced in sub-Saharan Africa will likely only use RTIs, not PIs
- In the developed world, the introduction of fusion inhibitors and integrase inhibitors suggests that cocktails may consist primarily of drugs that prevent viral infection of a T cell.

RTI=Reverse transcriptase inhibitor
PI=Protease inhibitor

PI-sparing regimens

- These are drugs that prevent the virus from transcribing its RNA onto host DNA
- Includes RTIs, fusion inhibitors and integrase inhibitors, but not protease inhibitors.

RTI=Reverse transcriptase inhibitor
DNA=deoxyribonucleic acid
RNA=ribonucleic acid

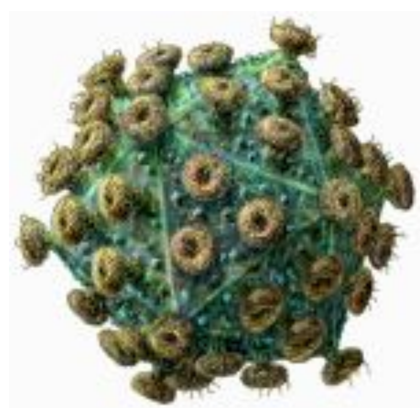


Fusion inhibitors block here
Integrase Inhibitors block here
Reverse Transcriptase Inhibitors block here
Protease Inhibitors block here
Entry
RNA dependent DNA synthesis
DNA Replication
DNA dependent DNA synthesis
Transcription
Mismatch DNA repair?
Translation
Assembly

The two strains

We assume two strains of the virus:

1. The wild-type strain will dominate in the absence of drugs
2. There is also a mutant strain that is a less efficient competitor, but more resistant to the drugs.



The basic idea

- Resistant mutants are not impervious to the drugs
- Rather, resistance confers a 5-50 fold resistance to the drugs
- Thus, if drug concentrations in the cell were sufficiently high, then even the mutant would be controlled.

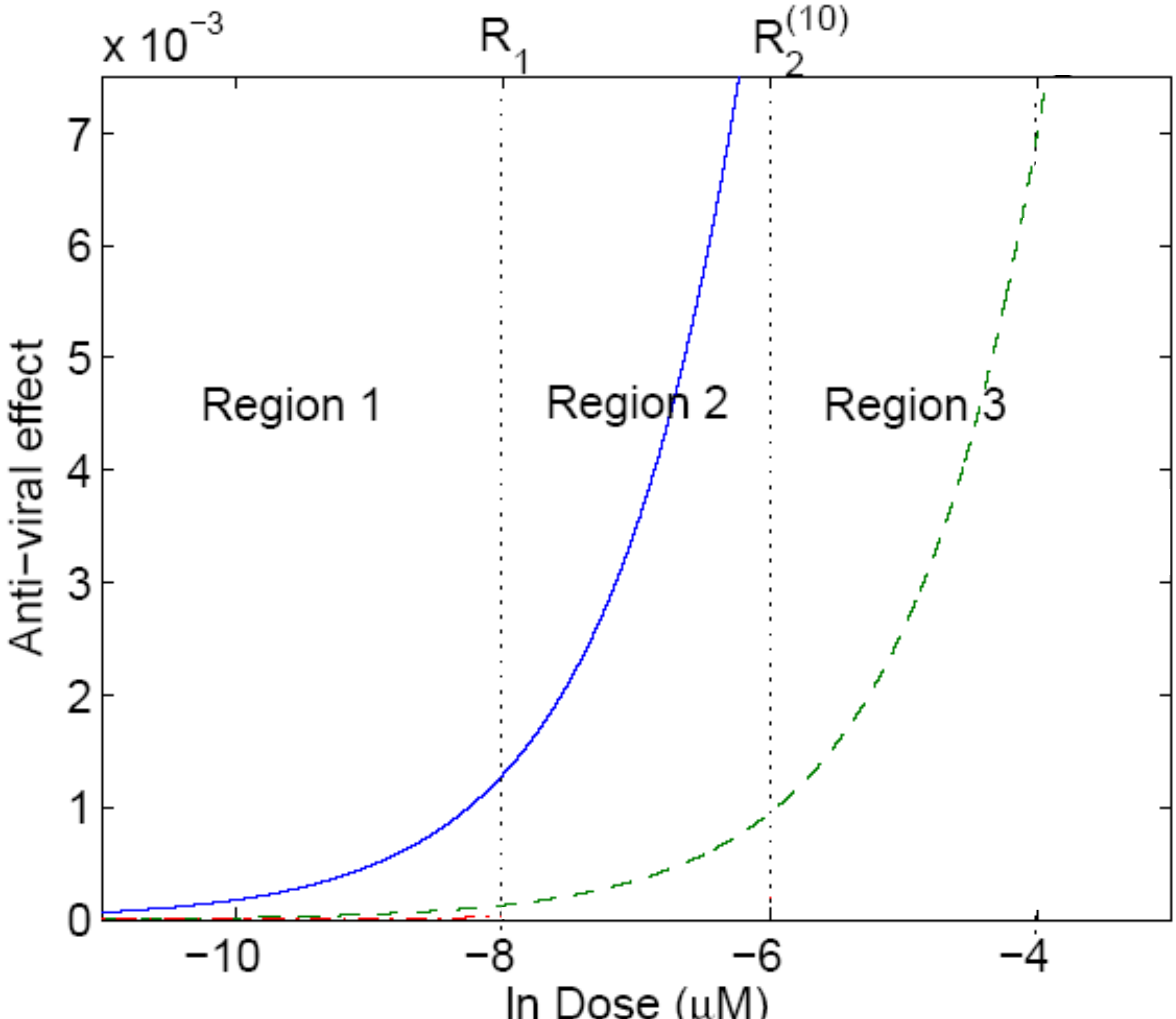
Drug dependence

- As drug levels fall, the wild-type strain is controlled, but the mutant may take hold
- When the drug falls to trough levels, the wild-type strain can regain its advantage
- Thus the amount of drug will determine how and when one, the other or neither strain gains dominance.

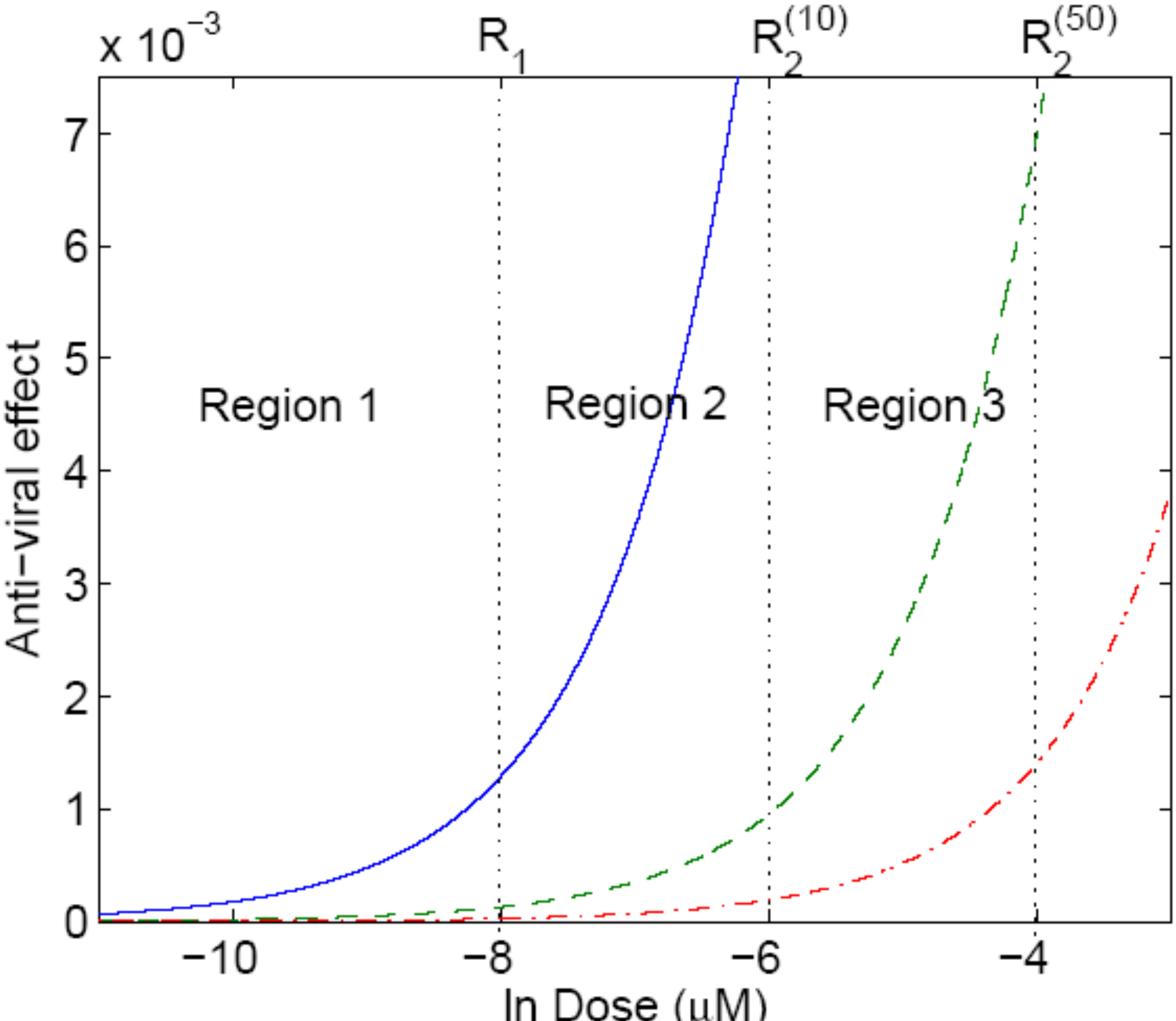
How to model something like this?

We consider three drug regimes:

- Region 1 (low): drugs are not sufficient to inhibit either strain
- Region 2 (medium): drugs will inhibit the wild type, but not the mutant
- Region 3 (high): drugs will inhibit both strains.



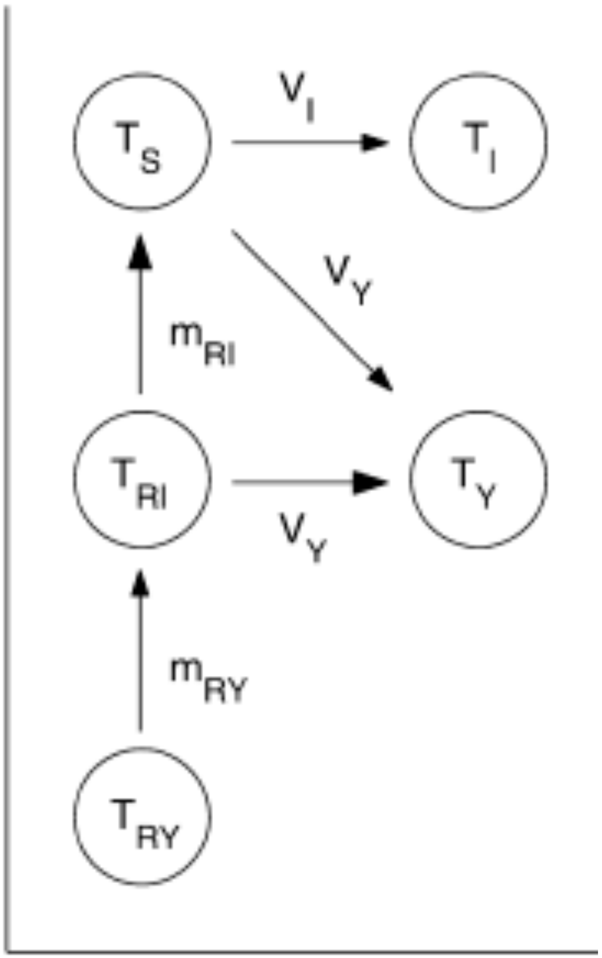
x 10^−3
R1
R2^(10)
Region 1
Region 2
Region 3
Anti−viral effect
ln Dose (μM)
0
1
2
3
4
5
6
7
−10
−8
−6
−4


x 10^-3
R_1
R_2^(10)
R_2^(50)
Region 1
Region 2
Region 3
Anti−viral effect
ln Dose (μM)
0
1
2
3
4
5
6
7
−10
−8
−6
−4

The model itself changes

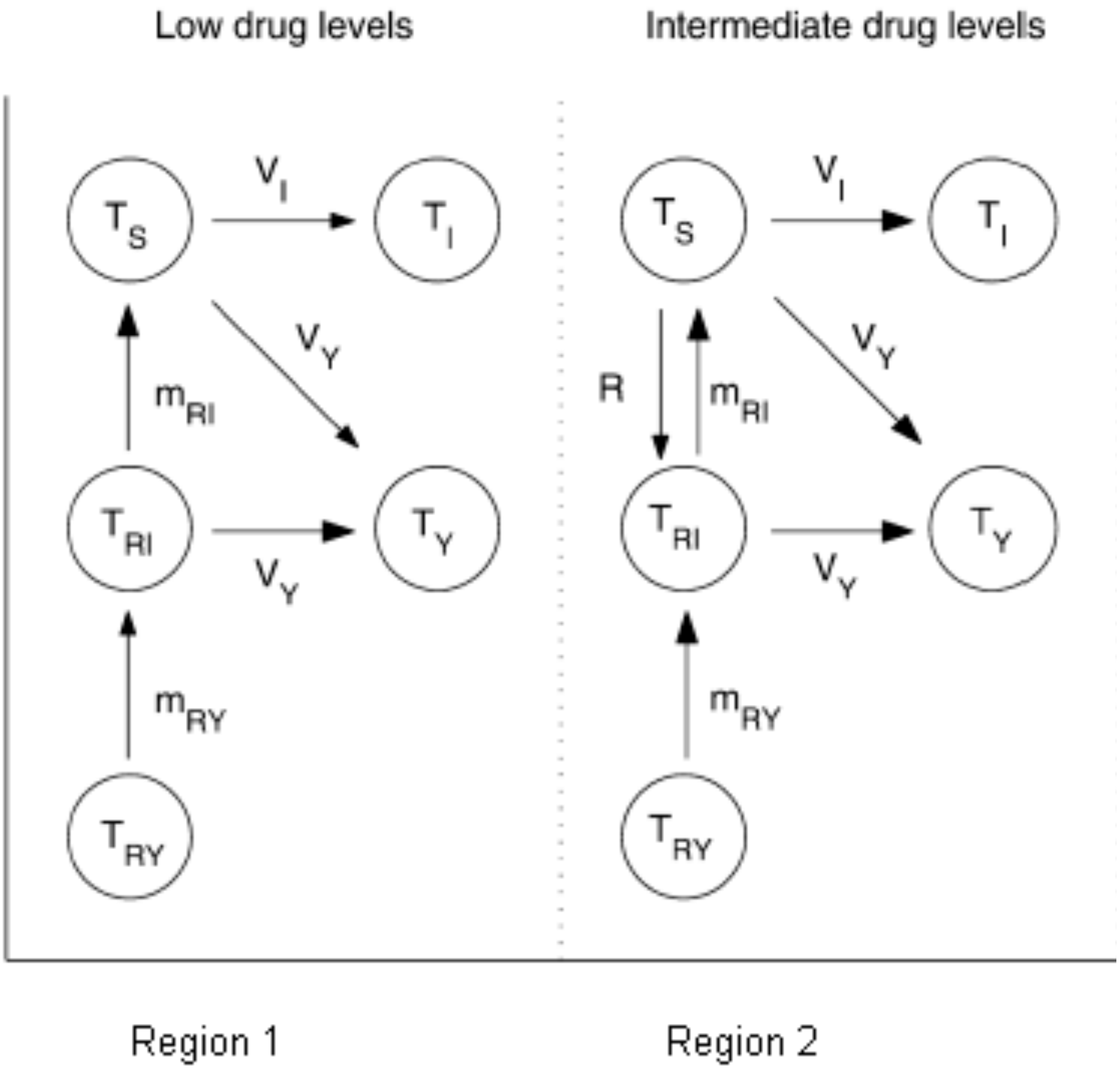
- Within each regime, the model itself will be different
- We have three models, connected by the drug behaviour
- Thus, as the drug levels change, so too does each model.

Low drug levels

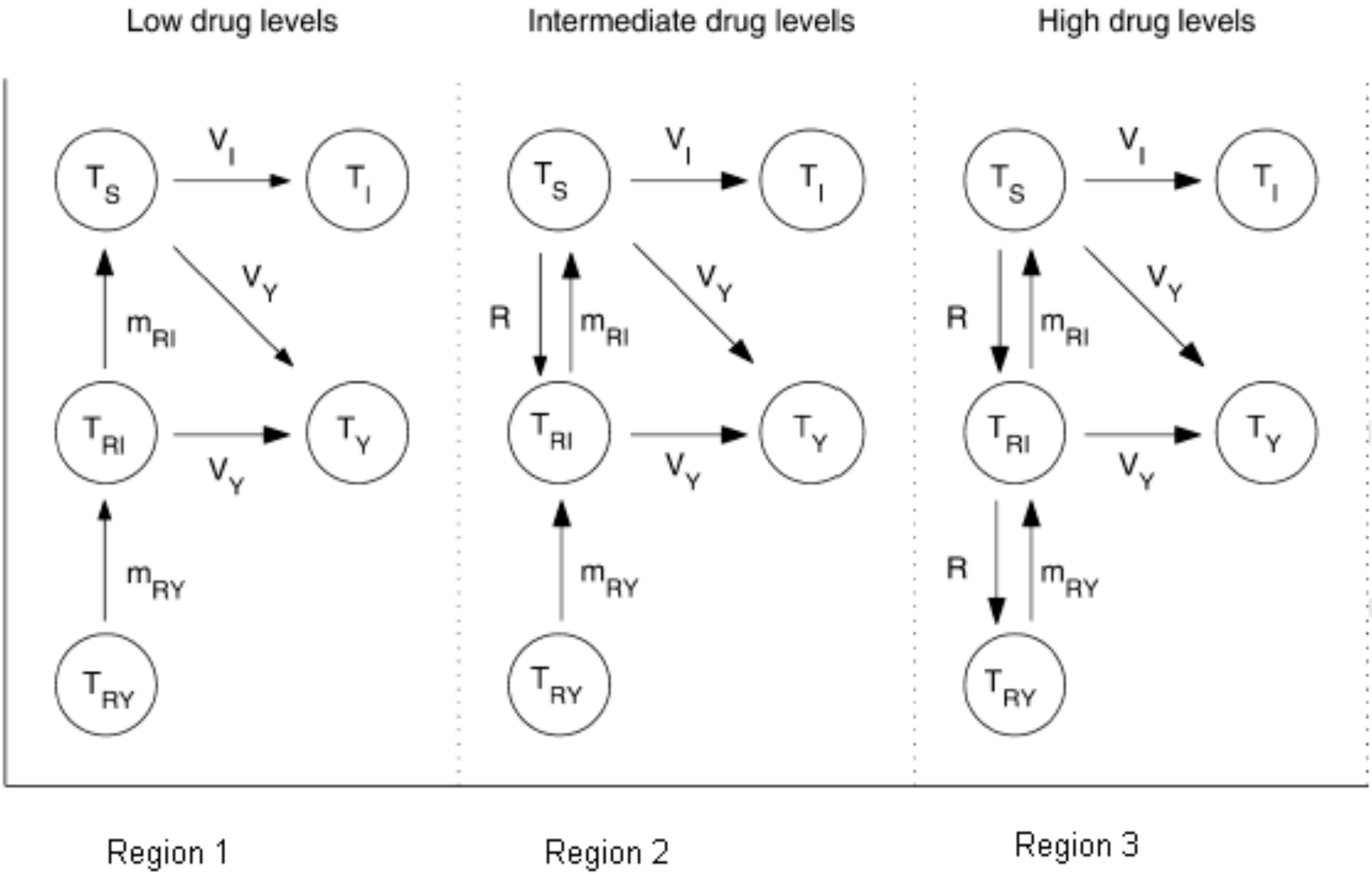


Region 1

T_S=Susceptible T cells T_I=Infected (wild type) T_Y=Infected (mutant)
T_{RI}=Intermediately inhibited T_{RY}=Highly inhibited V_I=wild-type virus
V_Y=mutant virus m_{RI}=waning rate m_{RY}=waning rate



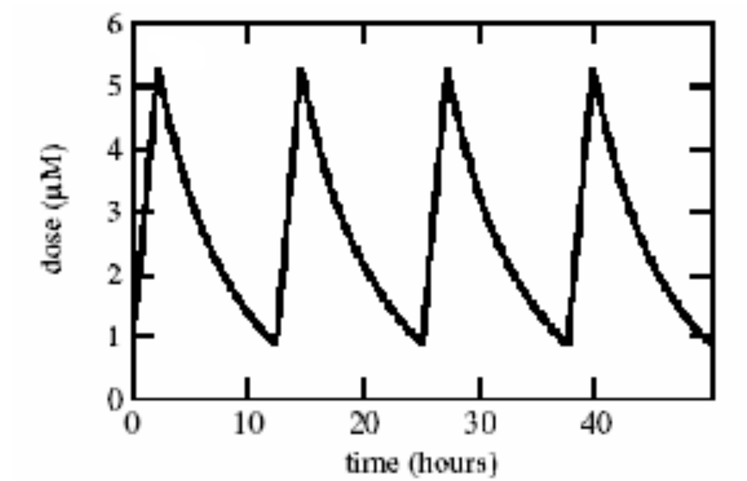
T_S=*Susceptible T cells* T_I=*Infected (wild type)* T_Y=*Infected (mutant)*
T_{RI}=*Intermediately inhibited* T_{RY}=*Highly inhibited* V_I=*wild-type virus*
V_Y=*mutant virus* m_{RI}=*waning rate* m_{RY}=*waning rate* *R=drug*



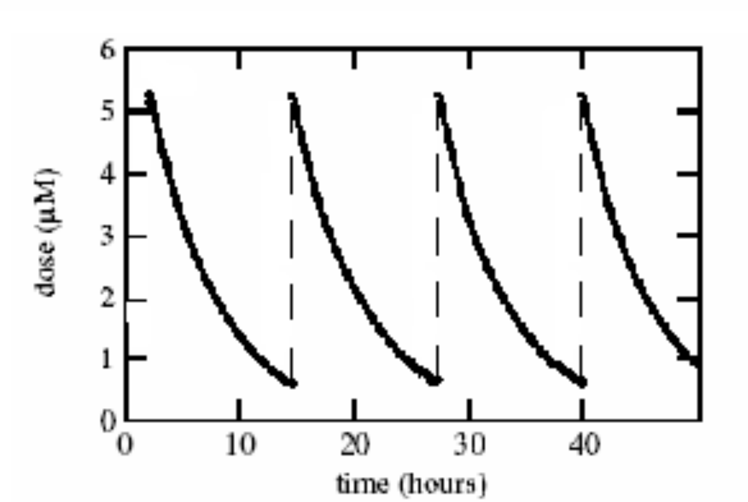
T_S=Susceptible T cells T_I=Infected (wild type) T_Y=Infected (mutant)
T_{RI}=Intermediately inhibited T_{RY}=Highly inhibited V_I=wild-type virus
V_Y=mutant virus m_{RI}=waning rate m_{RY}=waning rate R=drug

Impulsive Differential Equations

- Assume drug effects are instantaneous
- That is, the time-to-peak is assumed to be negligible



- This results in a system of *impulsive differential equations*.



Impulsive effect

- According to impulsive theory, we can describe the nature of the impulse at time r_k via the difference equation

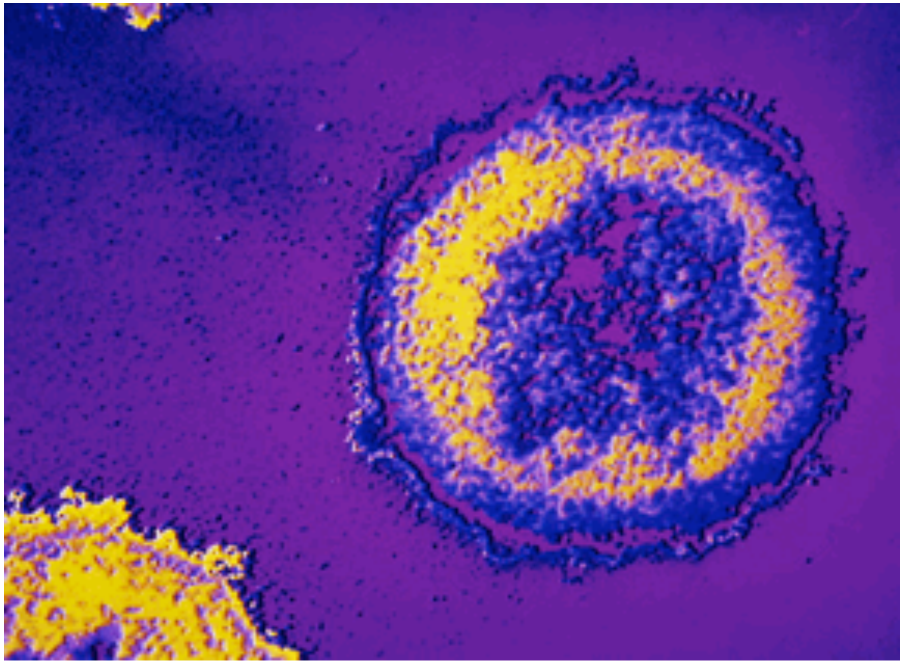
$$\Delta y \equiv y(r_k^+) - y(r_k^-) = f(r_k, y(r_k^-))$$

Difference equation

Depends on the time of impulse and the state immediately beforehand.

Impulsive DEs

- Solutions are continuous for $t \neq r_k$
- Solutions undergo an instantaneous change in state when $t = r_k$.



Thousands of HIV particles emerging from an infected T-cell

r_k=*impulse time*

Putting it together

- The model thus consists of a system of ODEs (virus and T cells) together with an ODE and a difference equation (drugs).

The model in Region 1 (low drugs)

$$\frac{dV_I}{dt} = n_I \omega T_I - d_V V_I - r_I T_S V_I$$

$$\frac{dV_Y}{dt} = n_I \omega T_Y - d_V V_Y - r_Y T_S V_Y - r_Y T_{RI} V_Y$$

$$\frac{dV_{NI}}{dt} = n_I (1-\omega)(T_I + T_Y) - d_V V_{NI}$$

$$\frac{dT_S}{dt} = \lambda - r_I T_S V_I - r_Y T_S V_Y - d_S T_S + m_{RI} T_{RI}$$

$$\frac{dT_I}{dt} = r_I T_S V_I - d_I T_I$$

$$\frac{dT_Y}{dt} = r_Y T_S V_Y - d_I T_Y + r_Y T_{RI} V_Y$$

$$\frac{dT_{RI}}{dt} = -r_Y T_{RI} V_Y - (d_S + m_{RI}) T_{RI} + m_{RY} T_{RY}$$

$$\frac{dT_{RY}}{dt} = -(d_S + m_{RY}) T_{RY}$$

T_S=Susceptible T cells T_I=Infected (wild type) T_Y=Infected (mutant) V_{NY}=noninfectious
T_{RI}=Intermediately inhibited T_{RY}=Highly inhibited V_I=wild-type virus d_j=clearance rates
V_Y=mutant virus m_j=waning rates λ=lymphic source n_I=# particles ω=infectious fraction
r_I=wild type infection rate r_Y=mutant infection rate

The model in Region 2 (intermediate drugs)

$$\frac{dV_I}{dt} = n_I \omega T_I - d_V V_I - r_I T_S V_I$$

$$\frac{dV_Y}{dt} = n_I \omega T_Y - d_V V_Y - r_Y T_S V_Y - r_Y T_{RI} V_Y$$

$$\frac{dV_{NI}}{dt} = n_I (1-\omega)(T_I + T_Y) - d_V V_{NI}$$

$$\frac{dT_S}{dt} = \lambda - r_I T_S V_I - r_Y T_S V_Y - d_S T_S - r_P T_S R + m_{RI} T_{RI}$$

$$\frac{dT_I}{dt} = r_I T_S V_I - d_I T_I$$

$$\frac{dT_Y}{dt} = r_Y T_S V_Y - d_I T_Y + r_Y T_{RI} V_Y$$

$$\frac{dT_{RI}}{dt} = r_P T_S R - r_Y T_{RI} V_Y - (d_S + m_{RI}) T_{RI} + m_{RY} T_{RY}$$

$$\frac{dT_{RY}}{dt} = -(d_S + m_{RY}) T_{RY}$$

T_S=Susceptible T cells T_I=Infected (wild type) T_Y=Infected (mutant) λ=lymphic source R=drug T_{RI}=Intermediately inhibited T_{RY}=Highly inhibited V_I=wild-type virus d_j=clearance rates V_Y=mutant virus V_{NY}=noninfectious m_j=waning rates n_I=# particles ω=infectious fraction r_I=wild type infection rate r_Y=mutant infection rate

The model in Region 3 (high drugs)

$$\frac{dV_I}{dt} = n_I \omega T_I - d_V V_I - r_I T_S V_I$$

$$\frac{dV_Y}{dt} = n_I \omega T_Y - d_V V_Y - r_Y T_S V_Y - r_Y T_{RI} V_Y$$

$$\frac{dV_{NI}}{dt} = n_I (1-\omega)(T_I + T_Y) - d_V V_{NI}$$

$$\frac{dT_S}{dt} = \lambda - r_I T_S V_I - r_Y T_S V_Y - d_S T_S - r_R T_S R + m_{RI} T_{RI}$$

$$\frac{dT_I}{dt} = r_I T_S V_I - d_I T_I$$

$$\frac{dT_Y}{dt} = r_Y T_S V_Y - d_I T_Y + r_Y T_{RI} V_Y$$

$$\frac{dT_{RI}}{dt} = r_R T_S R - r_Y T_{RI} V_Y - (d_S + m_{RI}) T_{RI} + m_{RY} T_{RY} - r_Q T_{RI} R$$

$$\frac{dT_{RY}}{dt} = r_Q T_{RI} R - (d_S + m_{RY}) T_{RY}$$

T_S=Susceptible T cells T_I=Infected (wild type) T_Y=Infected (mutant) λ=lymphic source R=drug T_{RI}=Intermediately inhibited T_{RY}=Highly inhibited V_I=wild-type virus d_j=clearance rates V_Y=mutant virus V_{NY}=noninfectious m_j=waning rates n_I=# particles ω=infectious fraction r_I=wild type infection rate r_Y=mutant infection rate

…with the (impulsive) dynamics of the drugs:

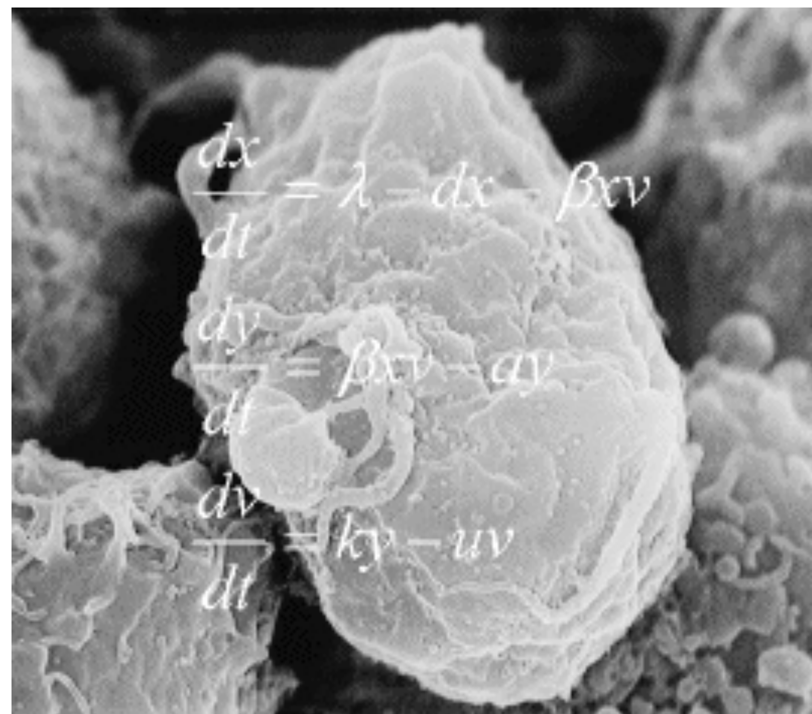
$$\frac{dR}{dt} = -d_R R \qquad t \neq t_k$$

$$\Delta R = \begin{cases} R^i & \text{if a dose is to be taken} \\ 0 & \text{if no dose is to be taken}\,. \end{cases}$$

R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

Limitations of the model

- Approximating the change in drug levels by impulsive differential equations means that results may be less accurate for short dosing intervals
- Dispersal and delay in intracellular dynamics may affect conclusions.



The drugs satisfy a recursion relation

$$R(t) = R(t_k^+)e^{-d_R(t-t_k)} \qquad t_k < t \leq t_{k+1}$$

$$R(t_k^+) = R(t_k^-) + R^i$$

R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

The drugs satisfy a recursion relation

$$R(t) = R(t_k^+)e^{-d_R(t-t_k)} \qquad t_k < t \leq t_{k+1}$$

$$R(t_k^+) = R(t_k^-) + R^i$$

Hence

R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

The drugs satisfy a recursion relation

$$R(t) = R(t_k^+)e^{-d_R(t-t_k)} \qquad t_k < t \le t_{k+1}$$

$$R(t_k^+) = R(t_k^-) + R^i$$

Hence

$$R(t_k^+) \rightarrow \frac{R^i}{1 - \mathrm{e}^{-d_\mathrm{R}\tau}}$$

R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

The drugs satisfy a recursion relation

$$\begin{aligned} R(t) &= R(t_k^+)e^{-d_R(t-t_k)} \qquad t_k < t \leq t_{k+1} \\ R(t_k^+) &= R(t_k^-) + R^i \end{aligned}$$

Hence

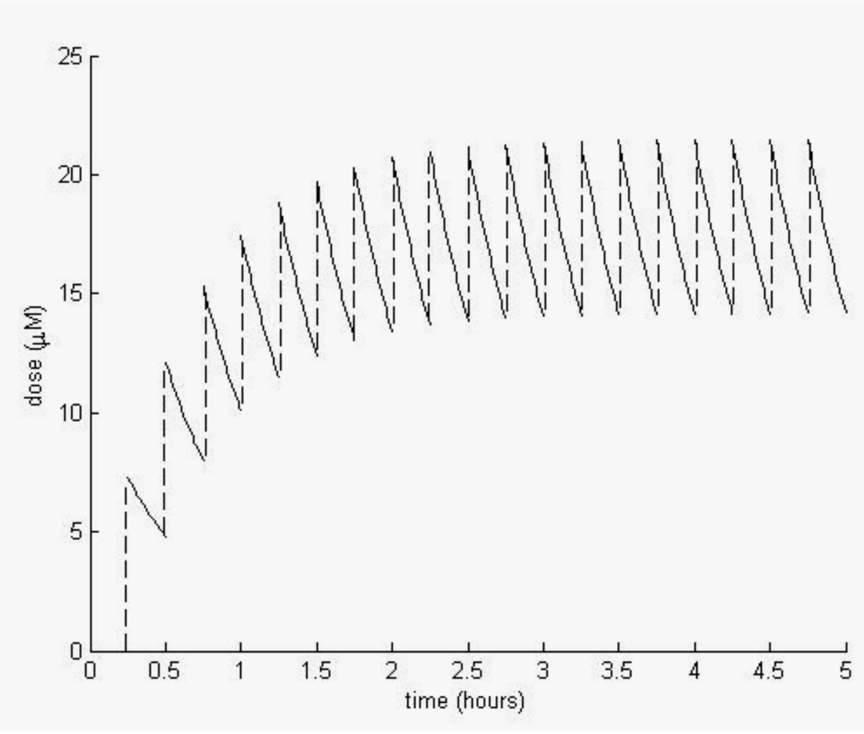
$$R(t_k^+) \rightarrow \frac{R^i}{1-\mathrm{e}^{-d_\mathrm{R}\tau}}$$

as $k \rightarrow \infty$, where $\tau = t_{k+1} - t_k$ is the dosing interval.

R=drug
d_R=decay rate
R^i=dosage
t_k=impulse time

Impulsive periodic orbit

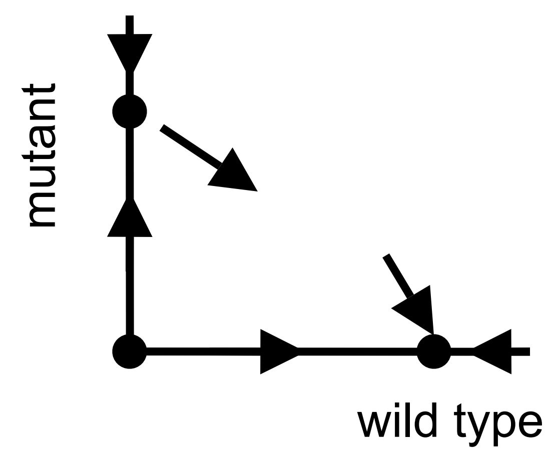
- Thus, for the drugs, there is a unique, positive impulsive periodic orbit with one impulse per cycle
- It can also be shown that the endpoints of each cycle monotonically approach the endpoints of this periodic orbit.



Region 1: Low drug levels

- Three equilibria: disease-free, wild type only, mutant only
- We can prove that the wild type equilibrium is stable and the others are unstable

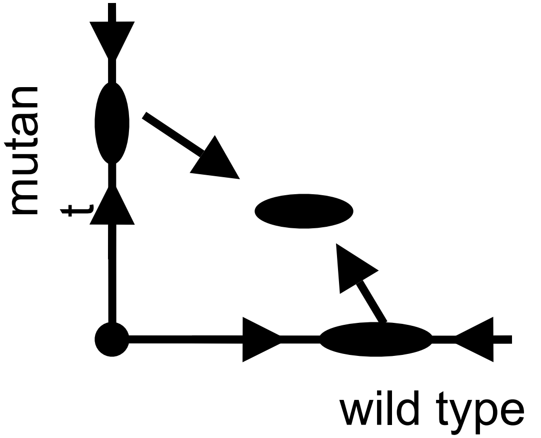
(Proof: See handout.)



Region 2: Intermediate levels

- There are no equilibria, due to impulses
- Four impulsive periodic orbits: disease-free, wild type only, mutant only and coexistence
- We can prove that the wild type and mutant coexist

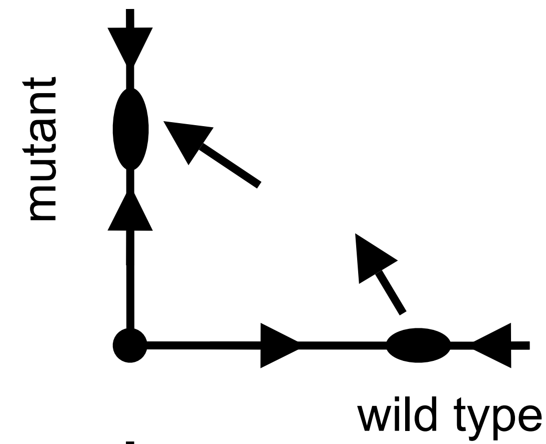
(Proof: See handout.)

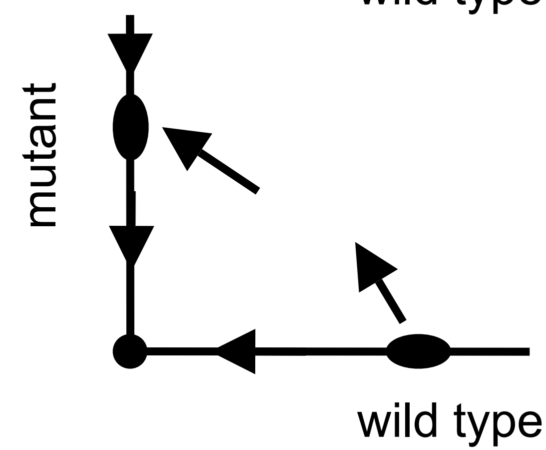


Region 3: High drug levels

- If $r_R \geq r_Q$, which we expect, then there are no interior orbits
- Three impulsive periodic orbits: disease-free, wild type only, mutant only
- We can prove that the disease-free orbit is unstable if and only if the wild type orbit exists

(Proof: See handout.)





Clearing the virus is possible

- Within Region 3, there is a region of viral elimination where the disease-free orbit is stable
- Otherwise the mutant alone dominates

(Proof: See handout).

Region 3=high drug levels

Summarizing

- For low drug levels, resistance does not emerge and the wild-type strain dominates
- For intermediate levels, resistance is guaranteed to emerge
- For high drug levels, either the mutant strain dominates, or both strains are eliminated.

Equilibrium T cell counts

- Region 1 (low drug levels):

$$\bar{T}_S + \bar{T}_I \quad = \quad \frac{\lambda}{d_I} + \frac{d_V(d_I - d_S)}{r_I(n_I\omega - d_I)} \ll \frac{\lambda}{d_S}$$

- Region 2 (intermediate levels):

Almost identical.

$$\bar{T}_S + T_I^* + T_Y^* + \bar{T}_{RI} \quad = \quad \frac{\lambda}{d_I} + \frac{d_V(d_I - d_S)}{r_Y(n_I\omega - d_I)} \ll \frac{\lambda}{d_S}$$

T_S=Susceptible T cells T_I=Infected (wild type) T_Y=Infected (mutant) λ=lymphic source
T_{RI}=Intermediately inhibited d_V= viral clearance rate d_S=uninfected T cell clearance rate
d_I=infected T cell clearance rate n_I=# particles ω=infectious fraction
r_I=wild type infection rate r_Y=mutant infection rate

Region 3

- What happens as the dosing interval shrinks to zero, or the dosage increases to infinity?
- Eventually we'll be in the region of viral elimination.

Which T cells dominate?

- We can prove the following:

Theorem. As $t \to \infty$ and either $\tau \to 0$, or $R^i \to \infty$, $T_S, T_I, T_Y, T_{RI} \to 0$ and $T_{RY} \to T_{RY}^{(\infty)}$ in region 3, where $T_{RY}^{(\infty)}$ satisfies

$$\frac{\lambda}{d_S + m_{RY}} \leq T_{RY}^{(\infty)} \leq \frac{\lambda}{d_S}$$

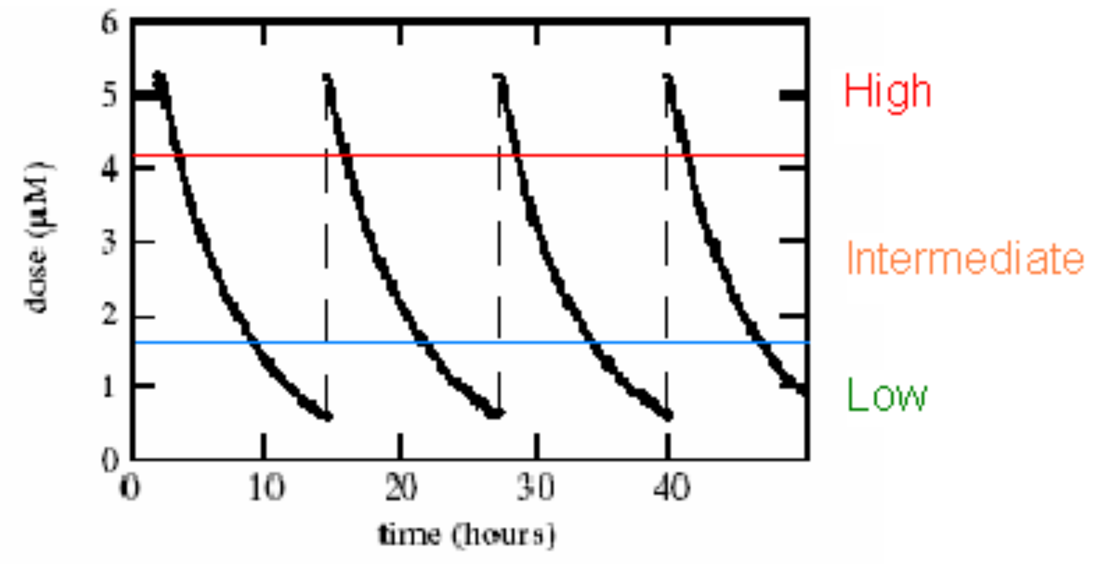
(Proof: See handout)

- These T cell levels are close to the levels in the uninfected immune system.

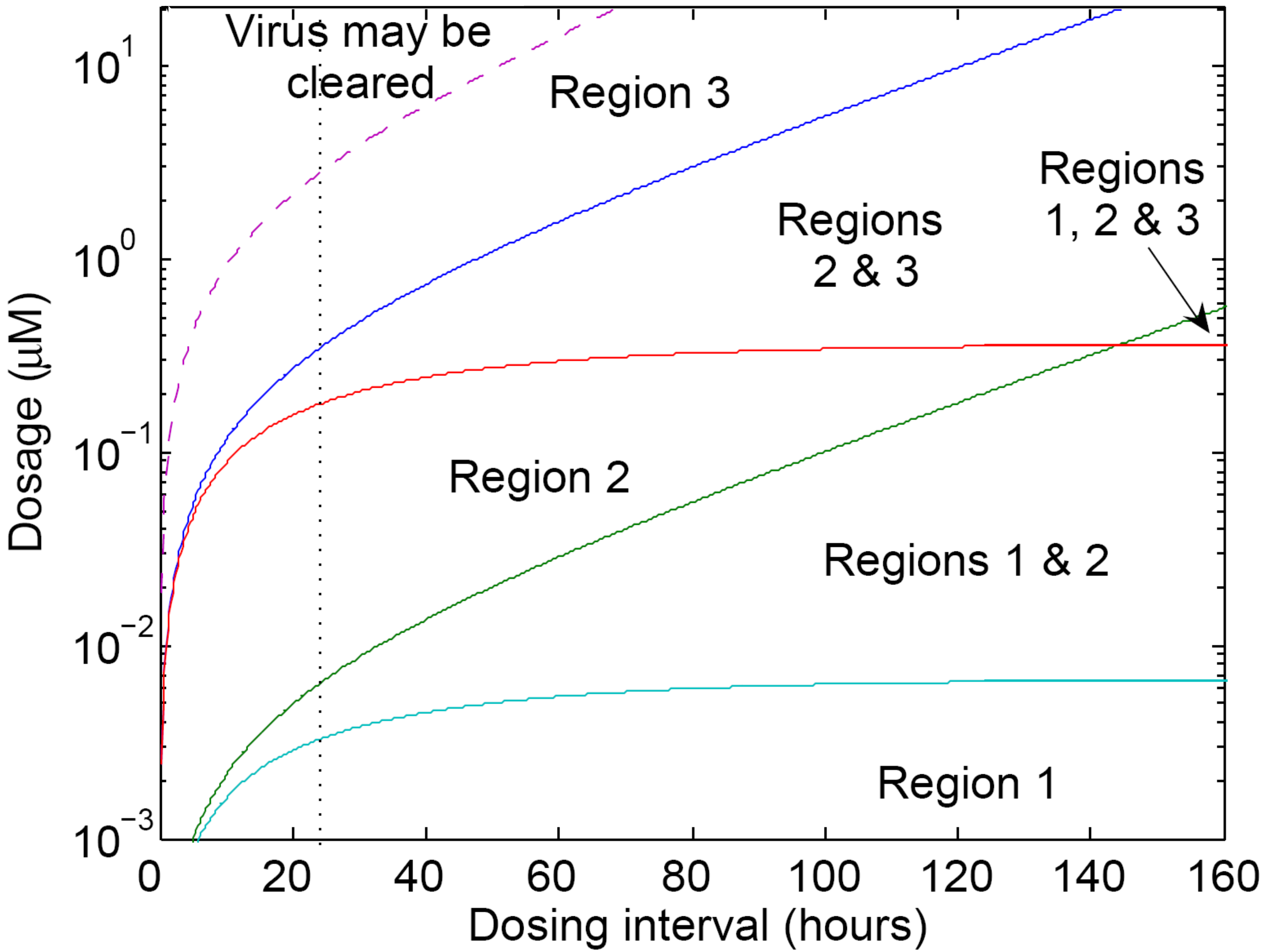
T_S=Susceptible T cells T_I=Infected (wild type) T_Y=Infected (mutant) m_{RY}=drug clearance rate
T_{RI}=Intermediately inhibited T_{RY}=Highly inhibited d_S=uninfected T cell clearance rate
λ=lymphic source τ =dosing interval R^i=dosage

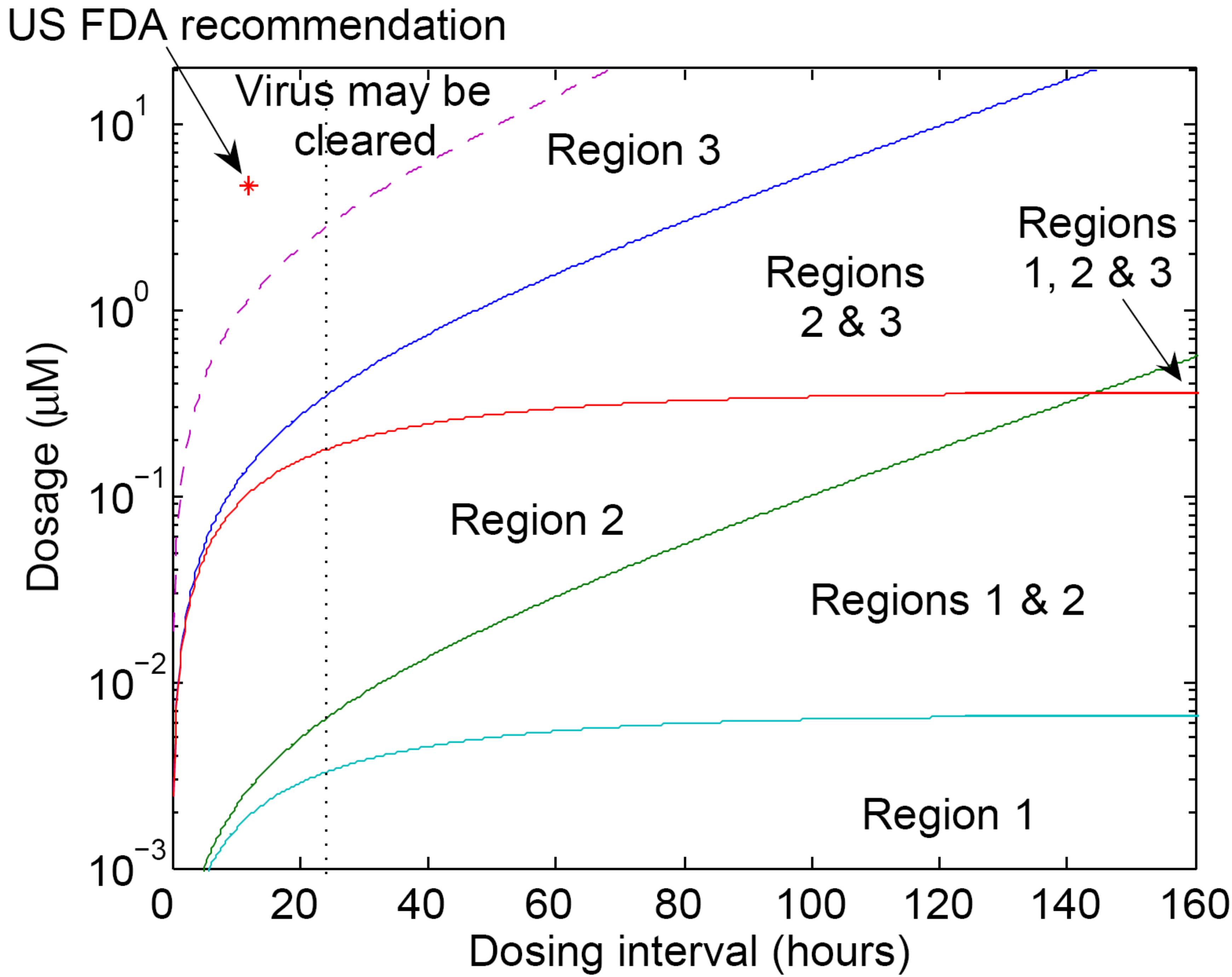
Putting it all together

- In practice, drug trajectories may cross one, two or all three regions



- Therefore, we examine parameter space for dosing intervals and dosages.


Virus may be cleared
Region 3
Regions 2 & 3
Regions 1, 2 & 3
Region 2
Regions 1 & 2
Region 1
Dosage (μM)
Dosing interval (hours)
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
0
20
40
60
80
100
120
140
160



US FDA recommendation
Virus may be cleared
Region 3
Regions 2 & 3
Regions 1, 2 & 3
Region 2
Regions 1 & 2
Region 1
Dosage (μM)
Dosing interval (hours)
10^1
10^0
10^-1
10^-2
10^-3
0
20
40
60
80
100
120
140
160

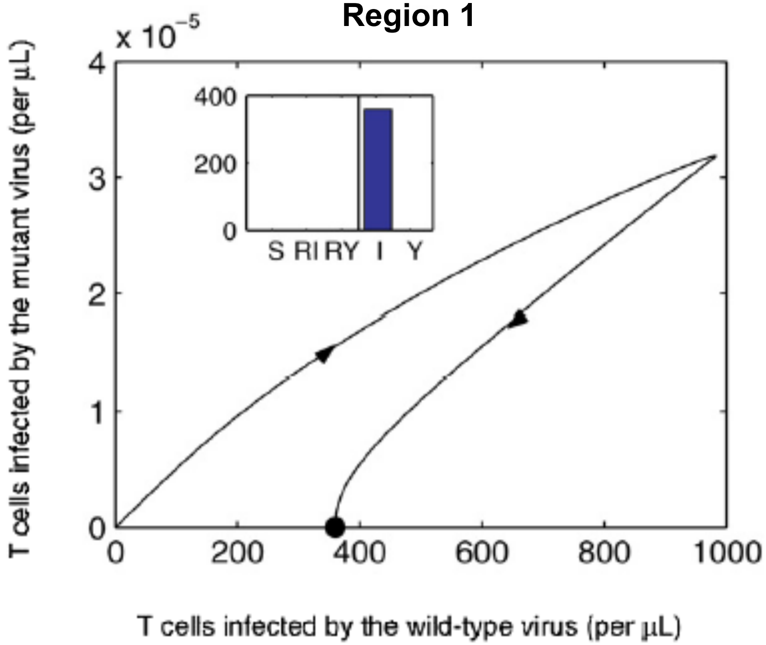
Outcome determined by parameter space

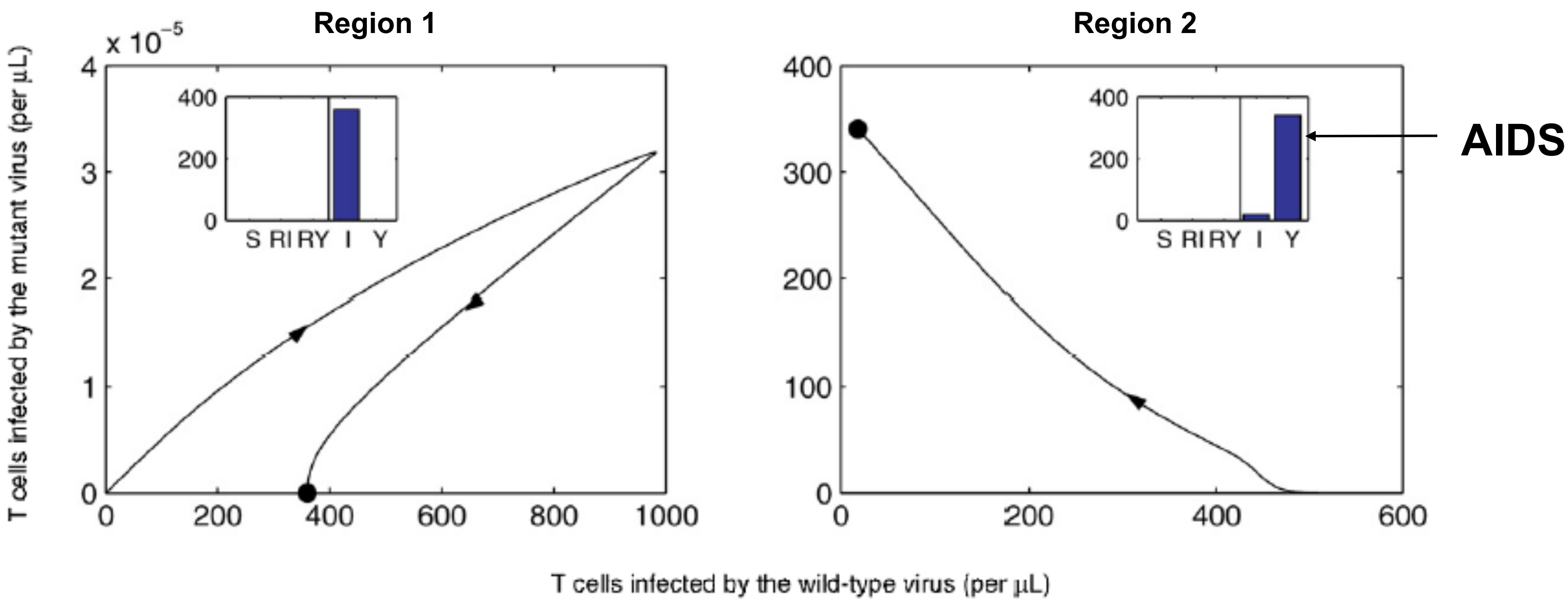
- The choice of dosing interval and dosage will completely determine which region(s) trajectories will ultimately lie in.

Simulations

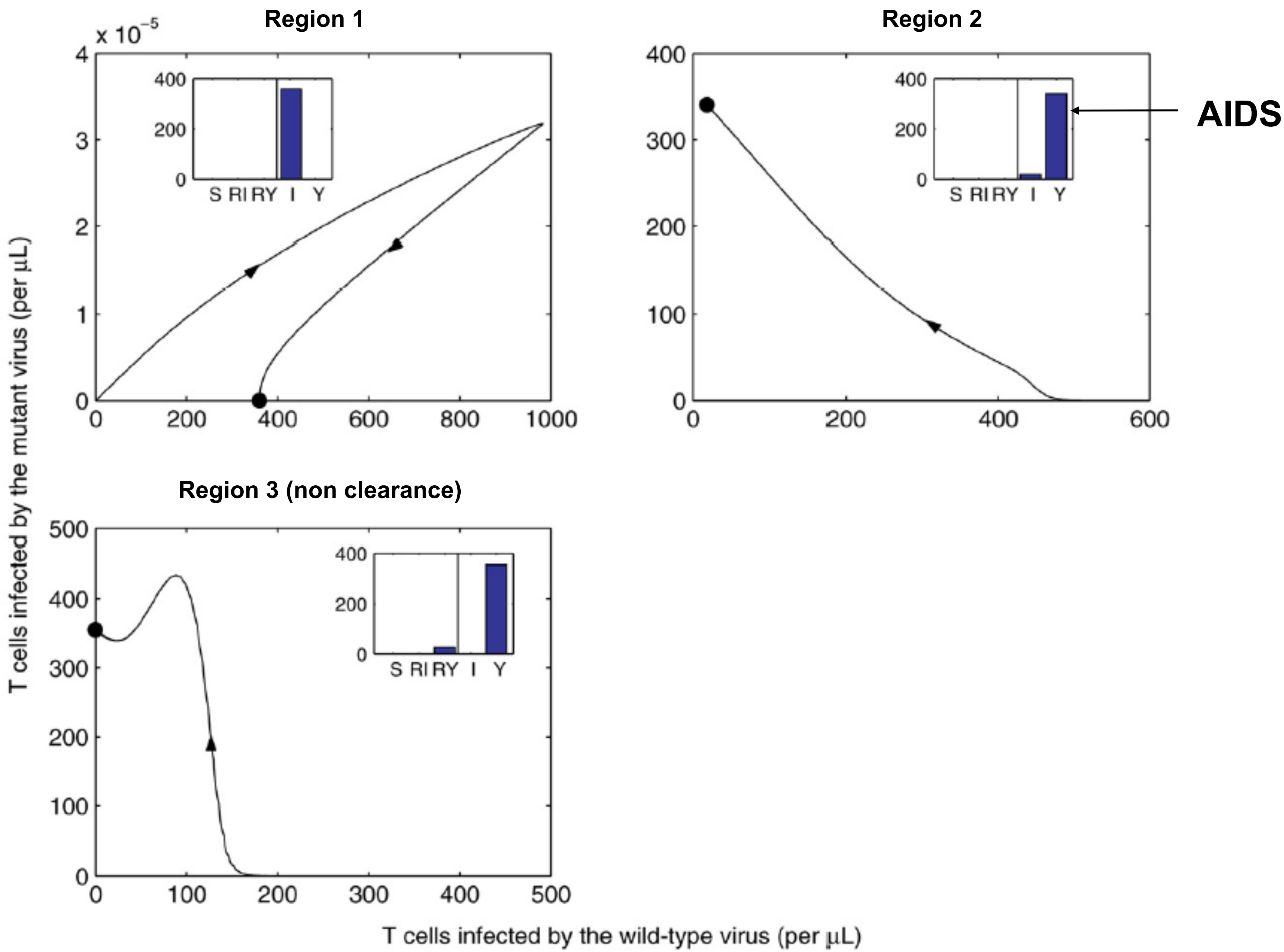
- Realistic parameters were simulated
- Only the dosing interval and the dosage were varied.

Region 1

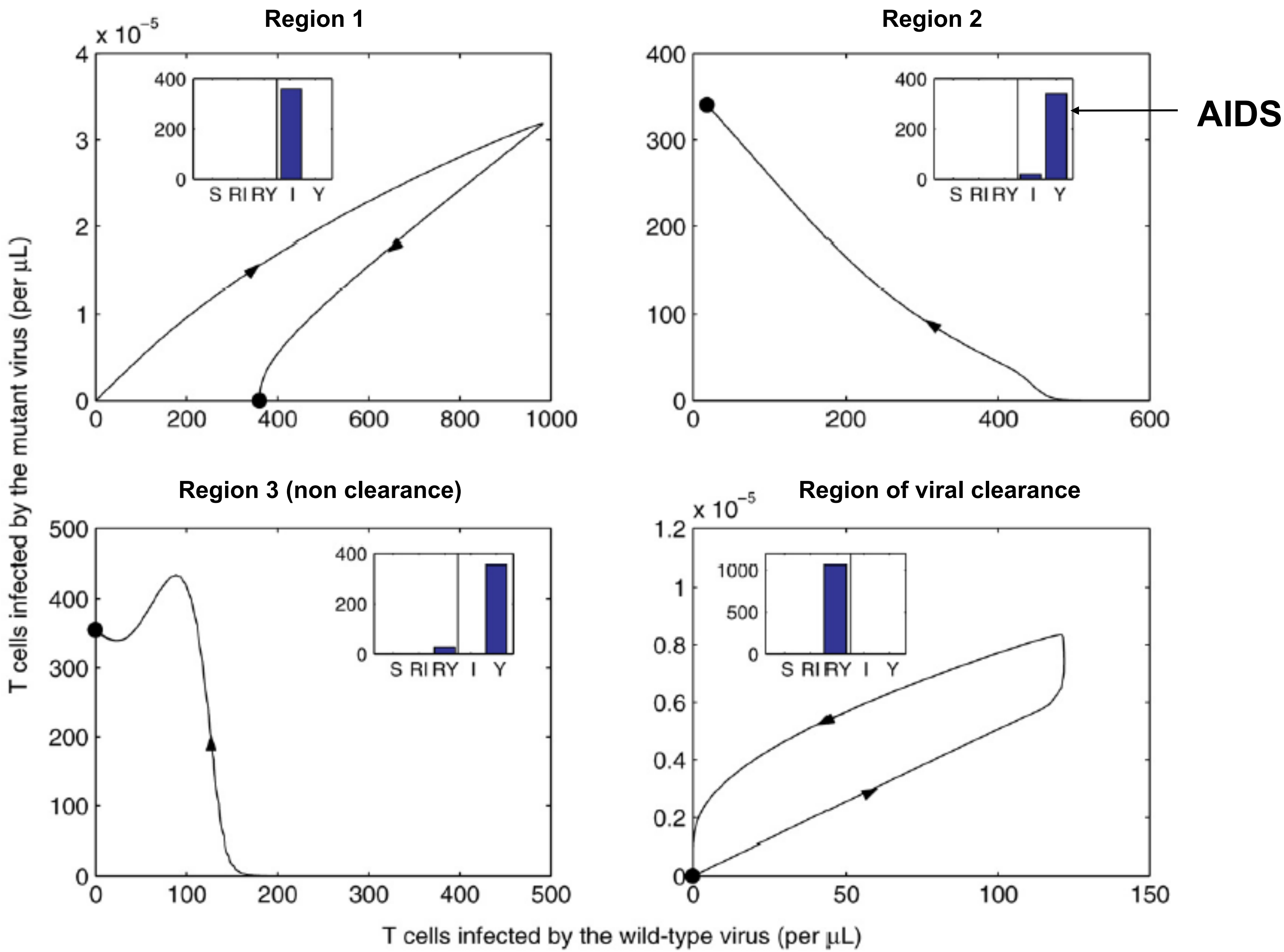

x 10^−5
4
3
2
1
0
400
200
0
S RI RY I Y
0
200
400
600
800
1000
T cells infected by the mutant virus (per μL)
T cells infected by the wild-type virus (per μL)



Region 1
Region 2
x 10^-5
T cells infected by the mutant virus (per μL)
4
3
2
1
0
0
200
400
600
800
1000
400
200
0
S RI RY I Y
400
300
200
100
0
0
200
400
600
400
200
0
S RI RY I Y
AIDS
T cells infected by the wild-type virus (per μL)



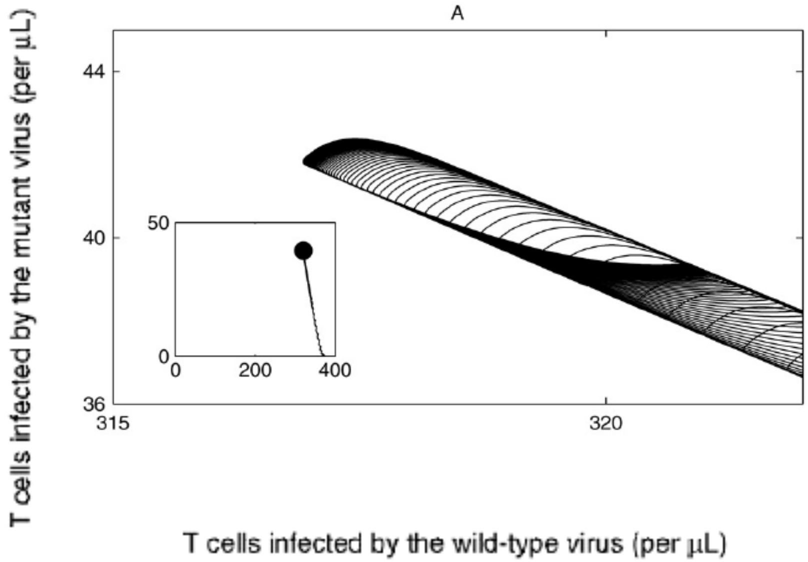
Region 1
x 10^-5
4
3
2
1
0
400
200
0
S RI RY I Y
0
200
400
600
800
1000
Region 2
400
300
200
100
0
400
200
0
S RI RY I Y
AIDS
0
200
400
600
Region 3 (non clearance)
500
400
300
200
100
0
400
200
0
S RI RY I Y
0
100
200
300
400
500
T cells infected by the mutant virus (per μL)
T cells infected by the wild-type virus (per μL)


Region 1
x 10^-5
Region 2
AIDS
Region 3 (non clearance)
Region of viral clearance
x 10^-5
S RI RY I Y
T cells infected by the mutant virus (per µL)
T cells infected by the wild-type virus (per µL)

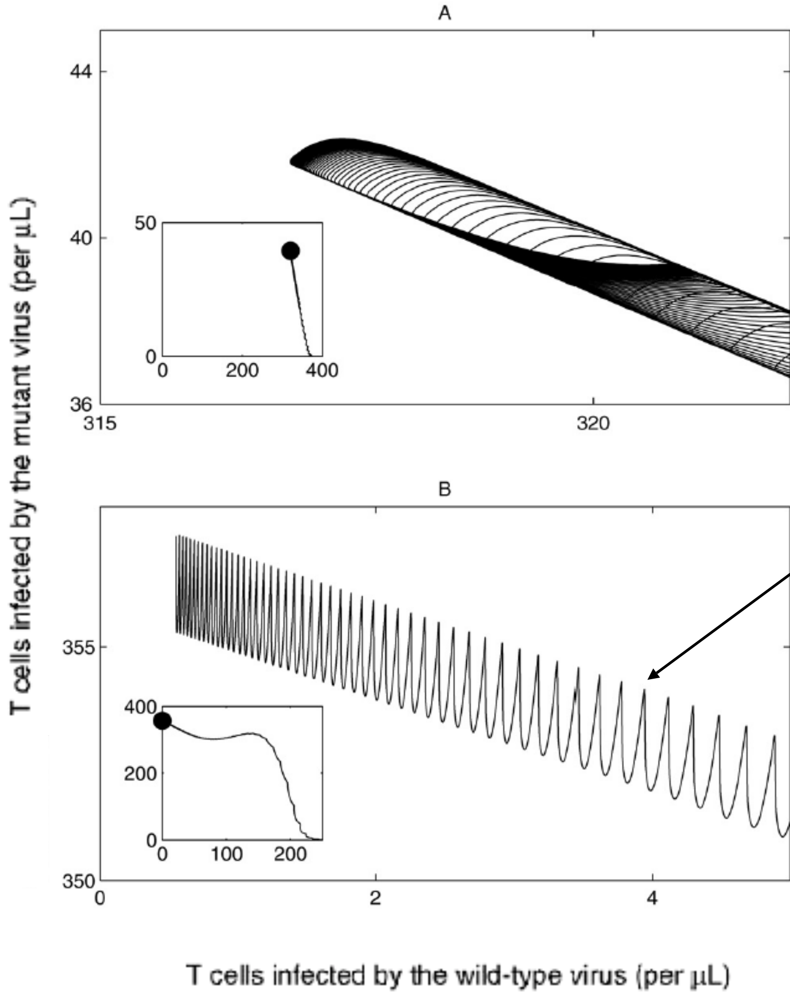
For single regions

Summarizing:

- Region 1 (low drugs): The wild type strain only
- Region 2 (intermediate drugs): The mutant strain mostly, with a small wild-type contribution
- Region 3 (high drugs): Either the mutant strain only, or the virus is eliminated.


A
44
40
36
315
320
50
0
0
200
400
T cells infected by the mutant virus (per μL)
T cells infected by the wild-type virus (per μL)

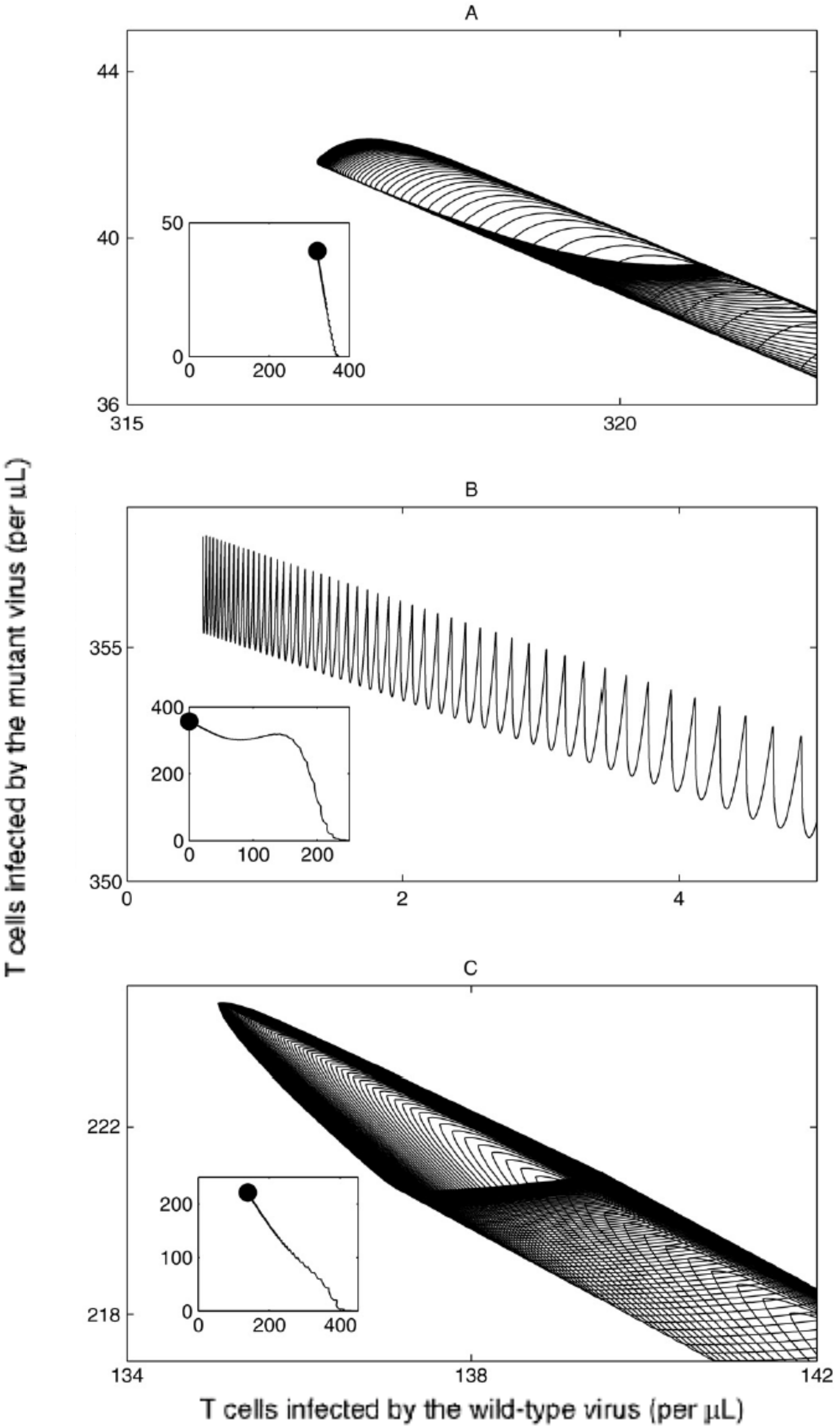
Regions 1 & 2



Regions 1 & 2

discontinuous derivatives

Regions 2 & 3



Regions 1 & 2

Regions 2 & 3

Regions 1, 2 & 3

For multiple regions

Summarizing:

- Regions 1 & 2: Coexistence of both strains, wild type dominates
- Regions 2 & 3: The mutant strain only
- Regions 1, 2 & 3: Coexistence, with high numbers of both types.

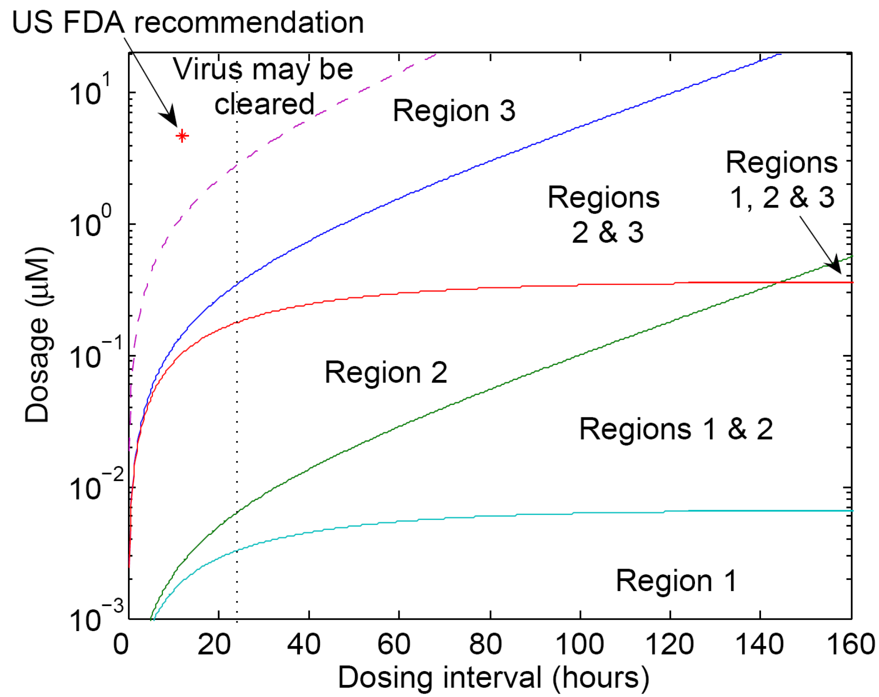
Region 1=low drug levels
Region 2=intermediate levels
Region 3=high drug levels

In summary

- If the drug levels are low, resistance will not emerge, but T cell counts are low
- For intermediate drug levels, resistance is guaranteed to emerge. T cell counts are similar to low drug levels
- For high drug levels, either the resistant strain will dominate, or the virus will be eliminated.

The question of adherence

- Thus, for perfect adherence, the virus is likely to be cleared



- What happens as adherence lapses?

"Clarification of the degree of adherence is the most urgent unanswered question in HIV research today"
-The U.S. Department of Health and Human Services.

Drug holidays

"Drug holidays" are extended breaks from the drugs. They may occur due to:

- lifestyle factors
- relief from side effects
- economic implications (especially in the developing world).


YOU HAVE
HIV.


YOU HAVE
HIV.
PEOPLE SAY
TAKE YOUR
MEDICATION.


YOU HAVE
HIV.
PEOPLE SAY
TAKE YOUR
MEDICATION.
THEY HAVE
NO IDEA.

Missing *h* doses

- Assuming perfect adherence, after the *n*th dose, drug levels satisfy

$$R(t_n^+) = \frac{R^i}{1 - e^{-d_R \tau}}$$

- To avoid Region 2 after *h* doses have been missed, we require

$$\frac{R^i \, e^{-h d_R \tau}}{1 - e^{-d_R \tau}} > R_2 \, .$$

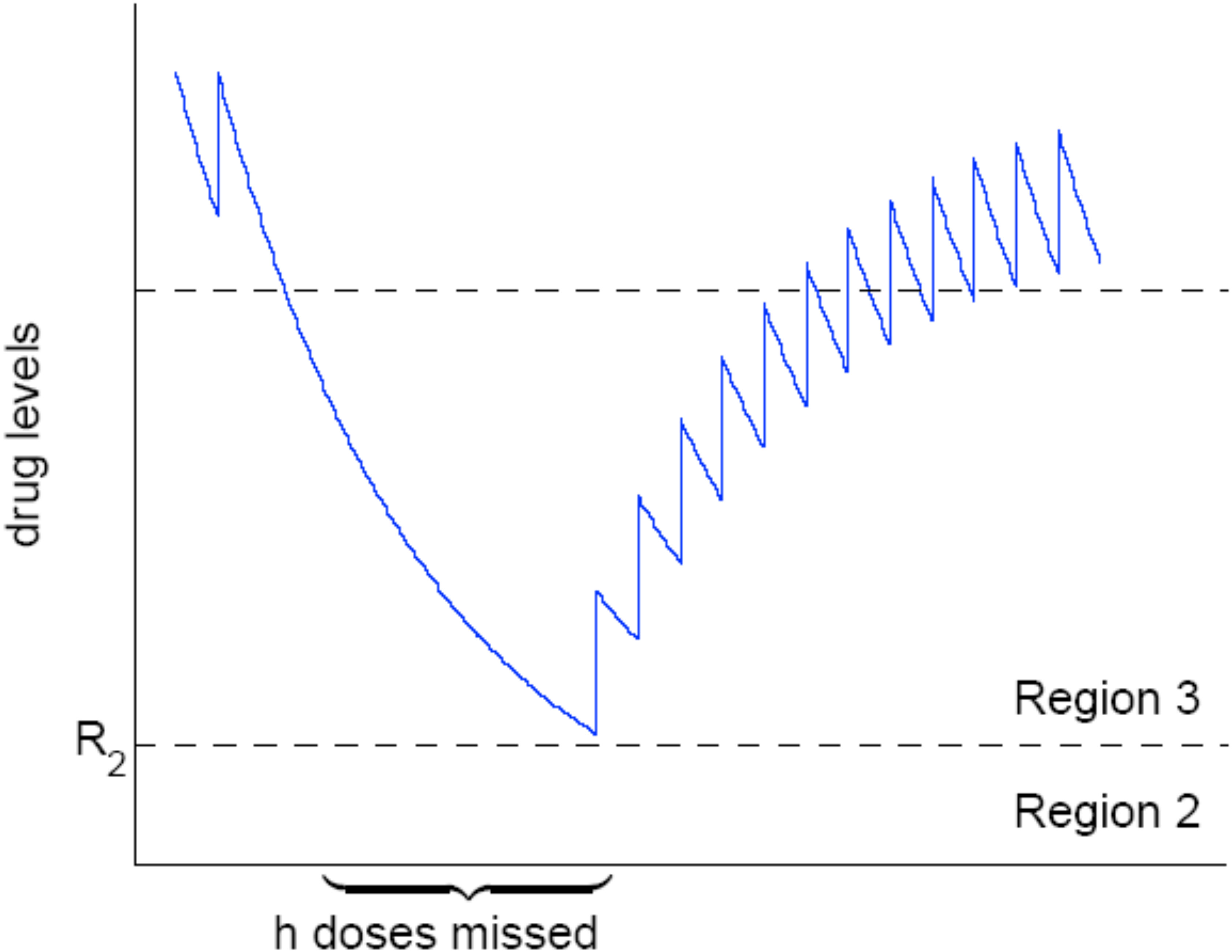
Region 2=intermediate drug levels R=drug R^i=dosage
d_R=drug decay rate τ =dosing interval R_2=Region 2 threshold

Avoiding resistance

- Thus the maximum number of missable doses satisfies

$$h < \frac{1}{d_R \tau} \log \frac{R^i}{R_2(1 - e^{-d_R \tau})} .$$

R^i=dosage d_R=drug decay rate τ =dosing interval
R_2=Region 2 threshold   h=# doses missed



drug levels
R$_2$
Region 3
Region 2
h doses missed

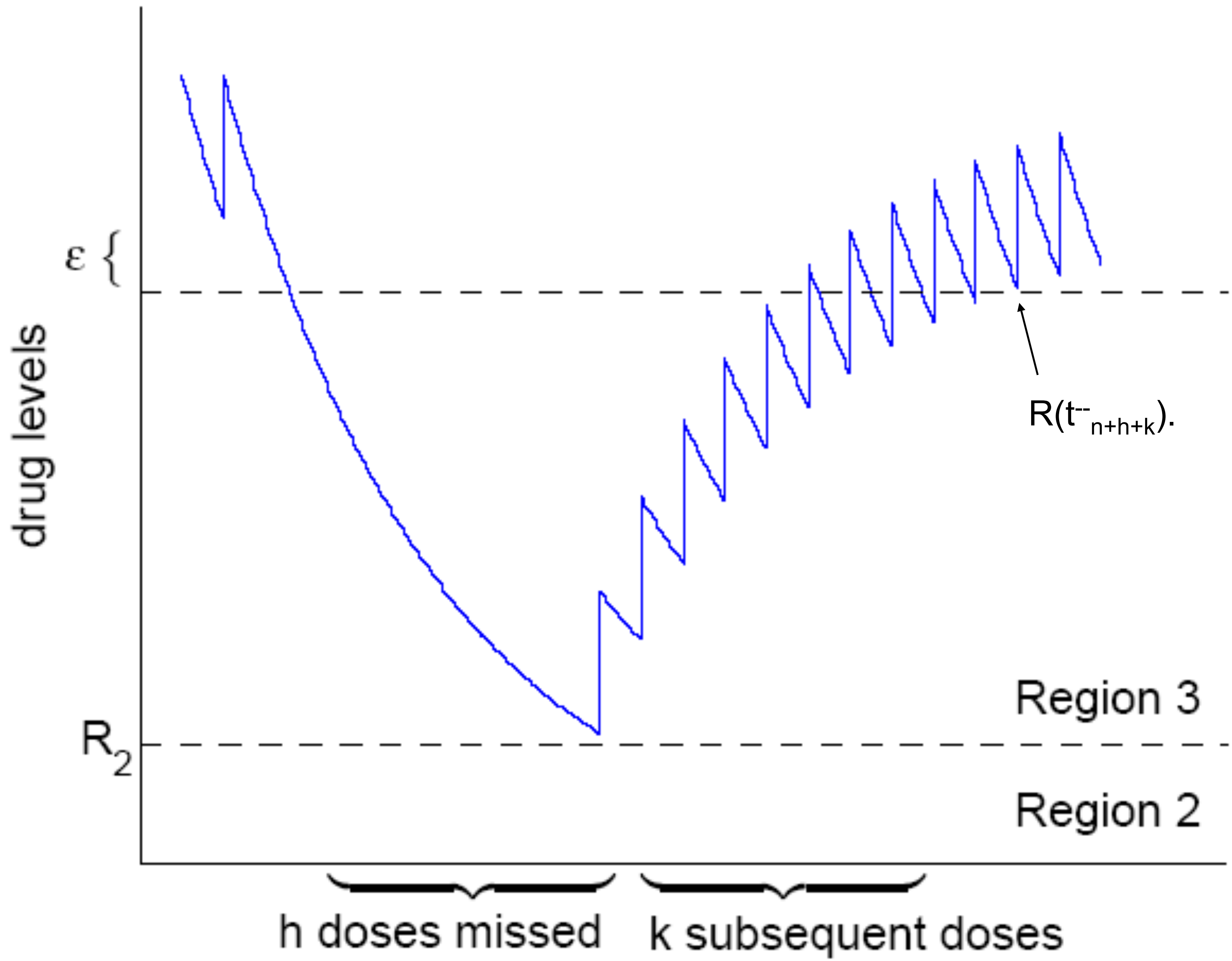
How many doses to take subsequently?

- Suppose *k* subsequent doses are taken in succession
- To return to drug levels approximating pre-interruption levels, we require

$$R(t_{n+h+k}^{-}) > \frac{R^i\, \mathrm{e}^{-d_\mathrm{R}\tau}}{1-\mathrm{e}^{-d_\mathrm{R}\tau}} - \epsilon,$$

for some required level of tolerance ε.

R^i=dosage d_R=drug decay rate τ =dosing interval
n=# doses previously taken h=# doses missed

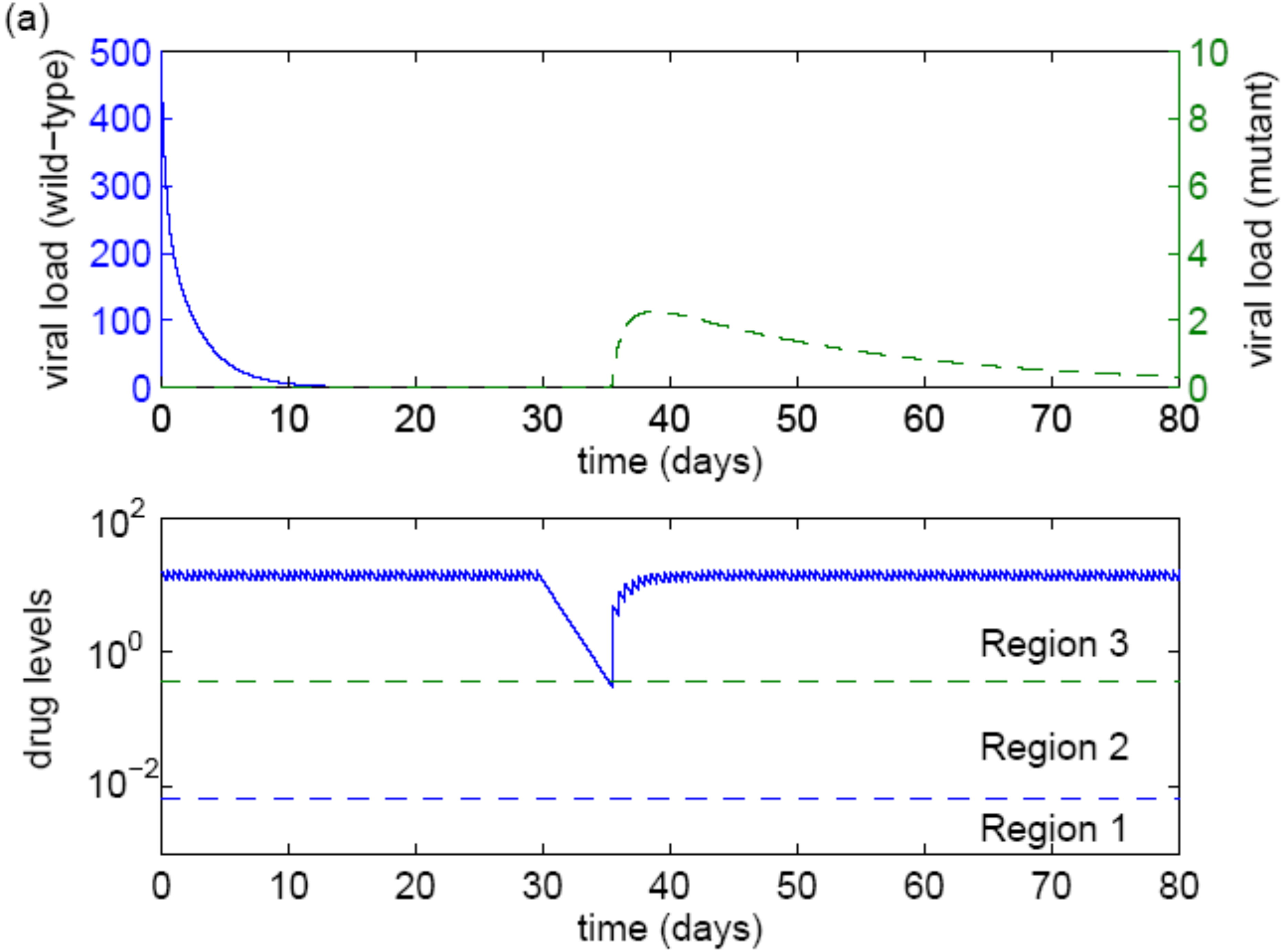


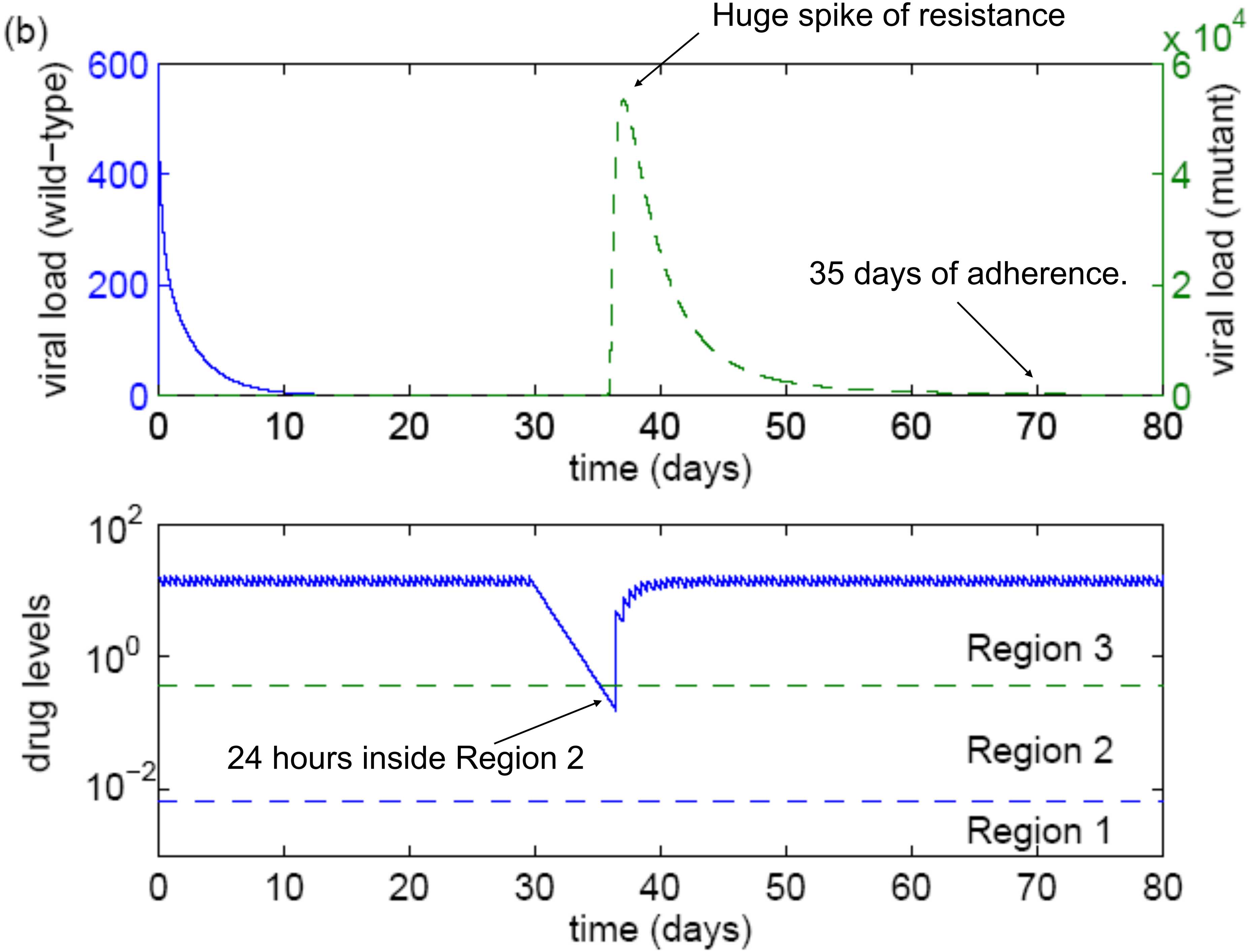
drug levels
ε
R(t⁻⁻n+h+k).
Region 3
R2
Region 2
h doses missed
k subsequent doses

E.g. Didanosine

- The nucleoside reverse transcriptase inhibitor Didanosine was simulated
- First the maximal number of missable doses were skipped
- Then the drug was allowed to enter Region 2 for 24 hours (equivalent to missing two further doses).

Region 2=intermediate levels


(a)
viral load (wild−type)
viral load (mutant)
500
400
300
200
100
0
10
8
6
4
2
0
0
10
20
30
40
50
60
70
80
time (days)
drug levels
10^2
10^0
10^{-2}
Region 3
Region 2
Region 1
0
10
20
30
40
50
60
70
80
time (days)


(b)
Huge spike of resistance
35 days of adherence.
viral load (wild−type)
viral load (mutant)
x 10^4
time (days)
drug levels
Region 3
Region 2
Region 1
24 hours inside Region 2
time (days)

A resistant spike

- Thus, entering Region 2 for 24 hours produced a spike of 60,000 μmol/L
- The resistant strain takes ~ 35 days to be eliminated, assuming perfect adherence subsequently.

Region 2=intermediate levels

Missable doses for approved drugs

- Similar methods were used to calculate the number of missable and subsequent doses for all PI-sparing drugs approved by the US FDA

- These levels all assumed 50-fold resistance.

PI=protease inhibitors

The number of missable and subsequent doses for all US FDA approved PI-sparing drugs (Smith, 2005)

drug	R^i (μM)	τ (days)	$T_{1/2}$ (h)	R_1 (μM)	$R_2^{(10)}$ (μM)	$R_2^{(50)}$ (μM)	missable	subsequent
Abacavir (ABC)	12	1/2	15	e^{-8}	e^{-6}	e^{-4}	13	9
Didanosine (ddI)	4.65	1/2	25	e^{-5}	e^{-3}	e^{-1}	11	14
Emtricitabine (FTC)	7.2	1	39	e^{-8}	e^{-6}	e^{-4}	16	11
Lamivudine (3TC)	6	1/2	17	e^{-5}	e^{-2}	e^{-1}	7	10
Stavudine (d4T)	2.144	1/2	7	e^{-6}	e^{-4}	e^{-2}	2	4
Tenofivir (TDF)	1.184	1	17	e^{-5}	e^{-3}	e^{-2}	1	4
Zalcitabine (ddC)	0.1008	1/3	3	e^{-8}	e^{-6}	e^{-4}	1	1
Zidovudine (ZDV)	4.24	1/3	3	e^{-12}	e^{-10}	e^{-8}	5	3
Delavirdine (DLV)	35	1/3	5.8	e^{-7}	e^{-5}	e^{-3}	7	5
Efavirenz (EFV)	12.9	1	45	e^{-8}	e^{-6}	e^{-4}	20	13
Nevirapine (NVP)	7.5	1/2	35	e^{-10}	e^{-7}	e^{-6}	40	20
Enfuvirtide (T20)	18.36	1/2	3.8	e^{-9}	e^{-7}	e^{-5}	3	3

dosage

dosing interval

halflife

Region 1 threshold

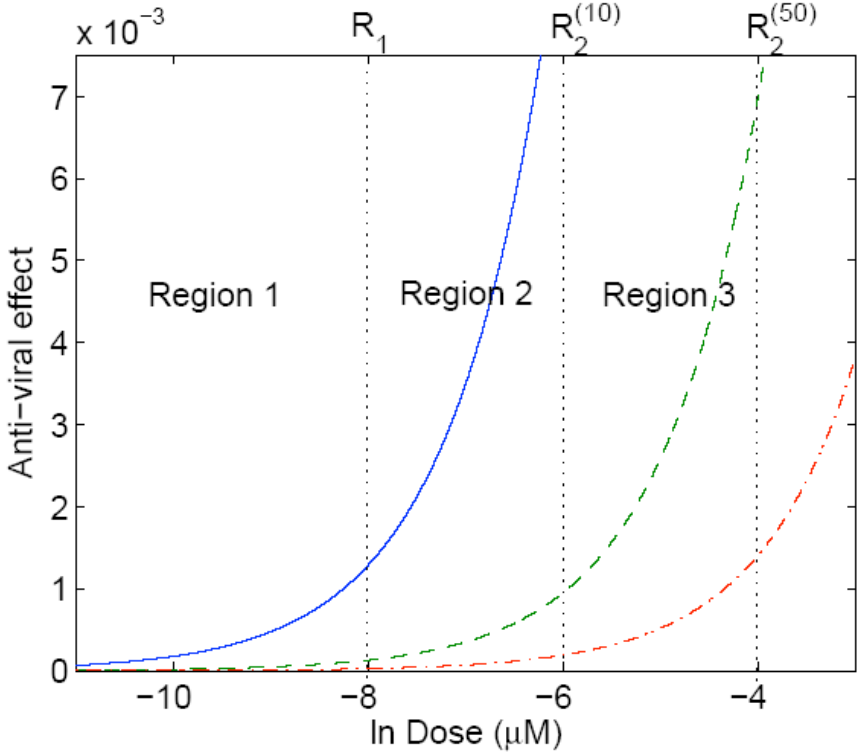
Region 2 threshold(s)

doses can be miss

doses that should be taken subsequently.

Multiple resistance

- If a drug has multiple resistant strains, calculate the Region 2 threshold for the highest strain
- E.g. if there are 10- and 50-fold resistant strains to Abacavir, use $R_2^{(50)}=e^{-4}$, rather than $R_2^{(10)}=e^{-6}$.



Region 2=intermediate levels R_2=Region 2 threshold

Combination therapy

For combination therapy, the results can be applied concurrently:

E.g. Trizivir consists of

- Abacavir (6.5 days of missable doses),
- Lamivudine (3.5 days) and
- Zidovudine (1.67 days).

Emerging resistance

- Resistance emerges to Zidovudine after 1.67 days
- After a further 3.5 days, resistance to Lamivudine emerges
- After 6.5 more days, resistance to Abacavir emerges

Therefore, this cocktail could be skipped for 11.67 days

(Probably an underestimate.)

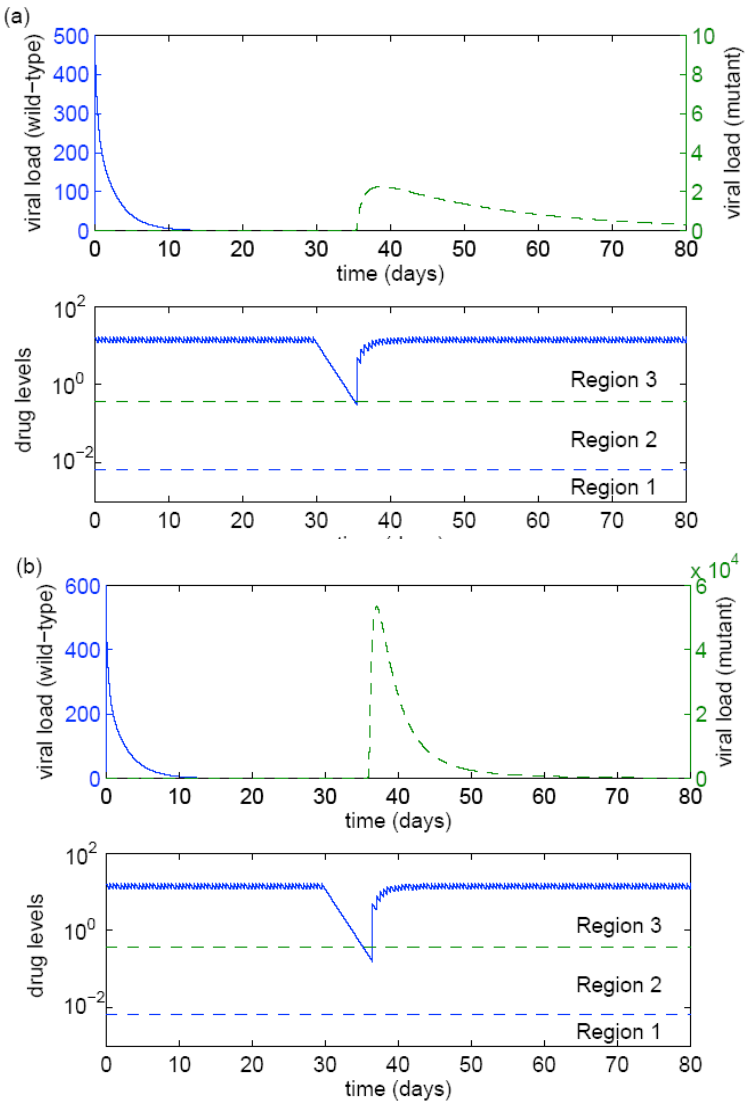
Experimental validation

- Results were compared to experiments in structured treatment interruptions (STIs)
- Patients interrupt therapy at fixed intervals only
- STIs have a delaying effect on the emergence of resistance

Nevertheless, results were broadly consistent with the timeframe.

Summary

- A small "drug holiday" may be acceptable, so long as sufficient doses are taken subsequently
- However, even 24 hours past the threshold of missable doses leads to extremely high resistance levels.



A general method

1. Identify the Region 2 threshold for the appropriate resistant strain
2. Calculate the number of missable doses
3. Calculate the number of subsequent doses

This method can be applied to any PI-sparing drug (including future drugs) for any level of resistance detected.

Region 2=intermediate levels PI=protease inhibitors