Basic PK-PD Principles of Proliferative and Circular Systems

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Outline

- Examples of proliferative and circular systems
- Some fundamental principles
  - Basic Reproductive Ratio (RR0)
  - Reproduction Minimum Inhibitory Concentration (RMIC)
- Derived basic PK-PD principles
- Some insights
- Conclusions

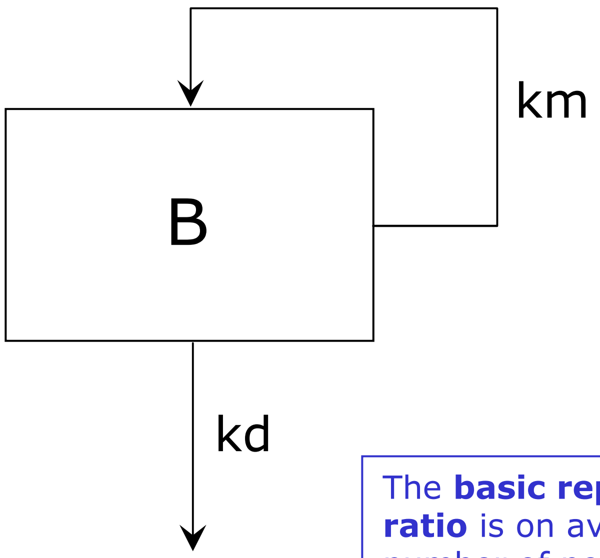
Some proliferative or circular systems

- Proliferative systems
  - Virus
  - Bacteria
  - Fungus
  - Cancer cell

- Circular systems
  - Inflammation
  - Allergy

A simple proliferative system to introduce some fundamental principles

Simple model



$$\frac{dB}{dt} = km.B - kd.B$$

$$\frac{dB}{dt} = (km - kd).B$$

km>kd → growth
km=kd → survival
km<kd → extinction

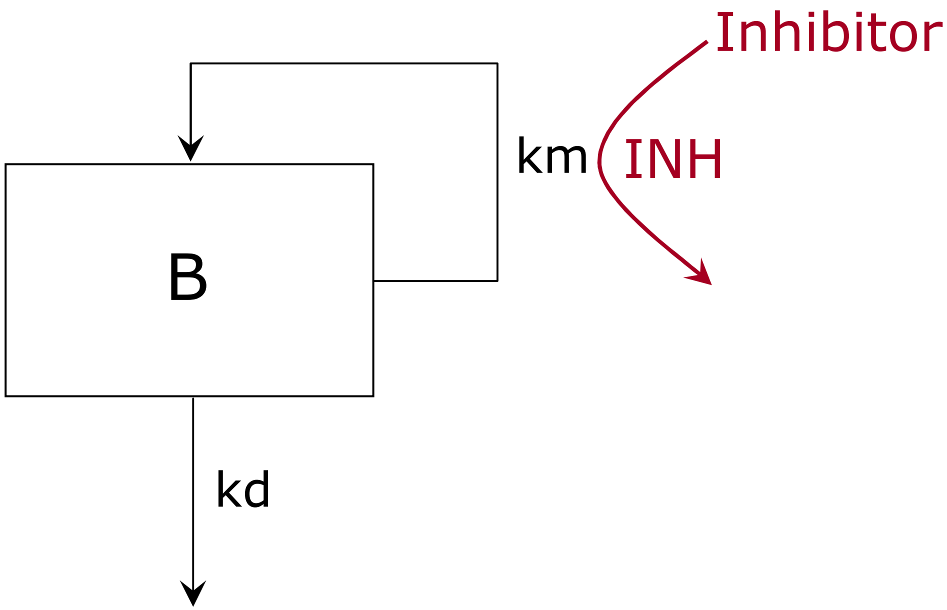
From a difference to a ratio

The **basic reproductive ratio** is on average the number of new Bs produced by one B during its life span

$$RR0 = \frac{km}{kd}$$

RR0>1 → growth
RR0=1 → survival
RR0<1 → extinction

A constant concentration of inhibitor leads to an apparent decrease of RR0 → $RR0_{INH}$



$$INH = \frac{IC}{IC_{50} + IC}$$

$$\frac{dB}{dt} = (1 - INH).km.B - kd.B$$

$$RR0_{INH} = \frac{(1 - INH).km}{kd}$$

$$\boxed{RR0_{INH} = (1 - INH).RR0}$$

$RR0_{INH} > 1$ → growth
$RR0_{INH} = 1$ → survival
$RR0_{INH} < 1$ → extinction

Proliferative systems in the presence of an inhibitor are characterized by the Reproduction Minimum Inhibitory Concentration (RMIC)

At inhibition leading to just survival

$$RR0_{INH} = 1 = (1 - INH).RR0$$

$$1 = \left(1 - \frac{IC}{IC_{50} + IC}\right).RR0$$

$$1 = \frac{IC_{50} + IC - IC}{IC_{50} + IC}.RR0$$

$$\frac{IC_{50} + IC}{IC_{50}} = RR0$$

$$\frac{IC_{50}}{IC_{50}} + \frac{IC}{IC_{50}} = RR0$$

$$\frac{IC}{IC_{50}} = RR0 - 1$$

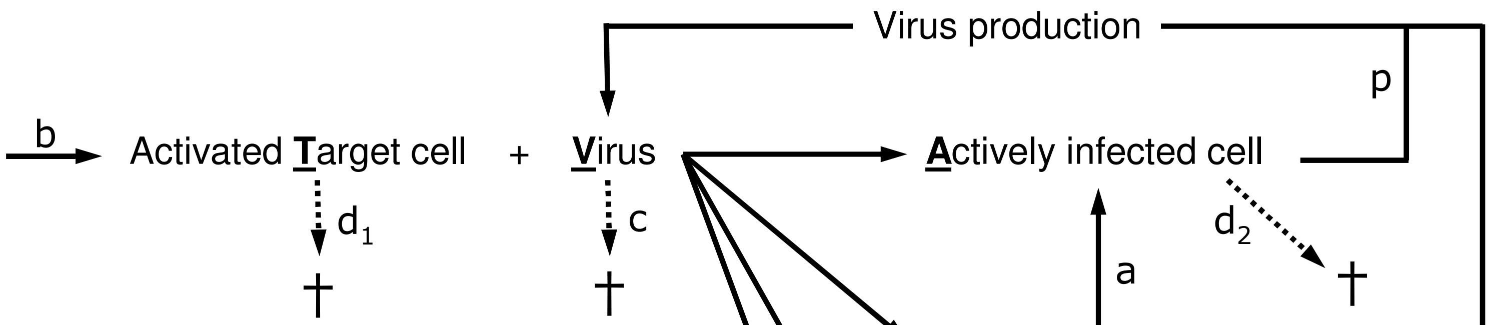
$$IC = (RR0 - 1).IC_{50}$$

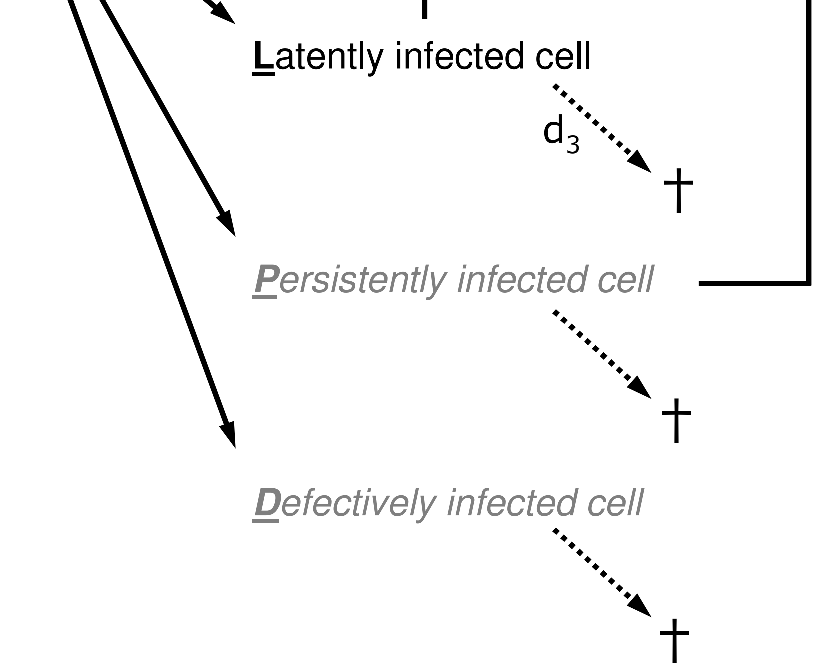
$$RMIC = (RR0 - 1).IC_{50}$$

$(RR0 - 1)$: System specific

IC_{50}: Drug specific

Viral dynamic models used in HIV are more complex. They are based on the predator-prey principle (Lotka-Volterra)





Target cell (activated CD4+ cells):

$dT/dt = b - d_1 \cdot T - i \cdot V \cdot T$

Actively infected cells (short-lived):

$dA/dt = f_1 \cdot i \cdot V \cdot T - d_2 \cdot A + a \cdot L$

Latently infected resting cells (long lived):

$dL/dt = f_2 \cdot i \cdot V \cdot T - d_3 \cdot L - a \cdot L$

Infectious virus (copies HIV-1 RNA):

$dV/dt = p.A - C.V$

(JAIDS, **26**, 397-404, 2001)

These more complex systems are also characterized by a Basic Reproductive Ratio (RR0)

The basic reproductive ratio (RR0) is defined as the average number of secondary viruses generated by viruses introduced into an uninfected environment

Factor for alive actively infected cells

Infection rate

$$RR0 = \frac{b}{d_1} \cdot i \cdot \frac{p}{c} \cdot \left(\frac{f_1}{d_2} + \frac{f_2 . a}{d_2 . (d_3 + a)} \right)$$

Number of activated cells in absence of virus

Circulating viruses by infected cell

If RR0 >1 the virus can establish an infection that will lead to an equilibrium between infected and uninfected cells

If RR0 < 1 the virus is unable to maintain the infection and will become extinct

An inhibitory E_{max} model decreasing the infection rate is usually used to describe the effect of antiretroviral compounds acting before DNA replication, leading to the same $RR0_{INH}$ function and RMIC formula

Target cell (activated CD4+ cells):

$dT/dt = b - d_1 \cdot T - (1\text{-}\mathbf{INH}) \cdot i \cdot V \cdot T$

Actively infected cells (short-lived):

$dA/dt = f_1 \cdot (1\text{-}\mathbf{INH}) \cdot i \cdot V \cdot T - d_2 \cdot A + a \cdot L$

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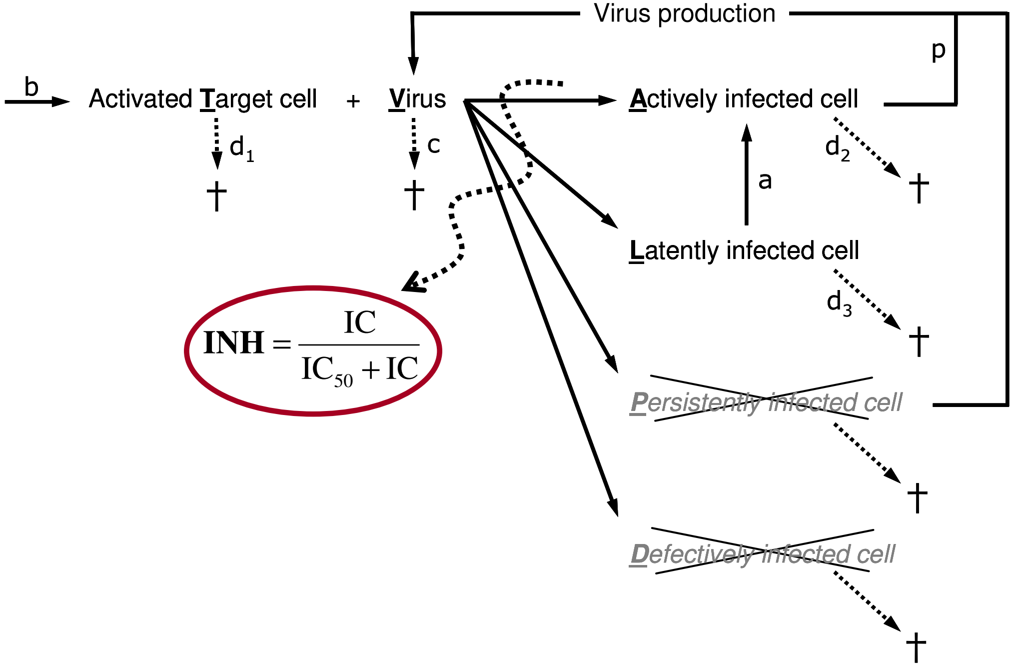


$$\mathbf{INH} = \frac{IC}{IC_{50} + IC}$$

$$RR0_{INH} = \frac{b}{d_1}.(1 - INH).i.\frac{p}{c}.\left(\frac{f_1}{d_2} + \frac{f_2.a}{d_2.(d_3 + a)}\right) = (1 - INH).RR0$$

$$RMIC = (RR0 - 1).IC_{50}$$

PK-PD principles derived from RR0 and RMIC (1)

- Depending on RR0, system survival (i.e. $RR0_{INH}=1$) can occur at different levels of inhibition and RMIC:
  - For RR0=2, $RR0_{INH}=1=2.(1-0.5)$, $RMIC=IC_{50}$
  - For RR0=10, $RR0_{INH}=1=10.(1-0.9)$, $RMIC=9*IC_{50}=IC_{90}$

- If *in vitro* and *in vivo* RR0 are different, *in vitro* and *in vivo* RMIC will also be different.

- RMIC is a joint distribution of RR0 and IC_{50} in the population.

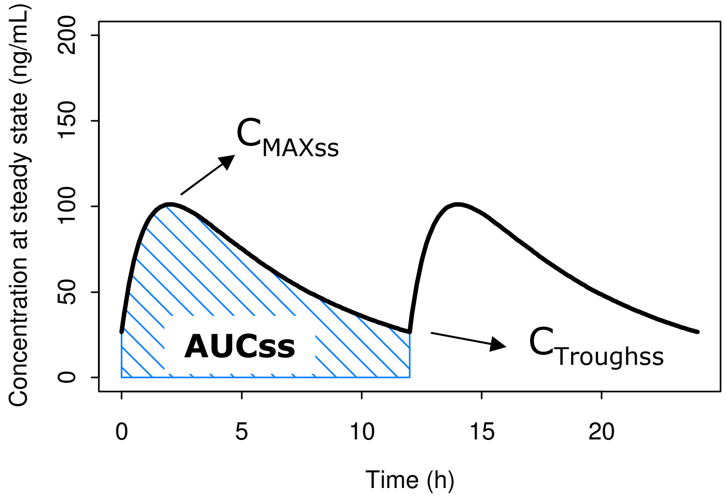
PK-PD principles derived from RR0 and RMIC (2)

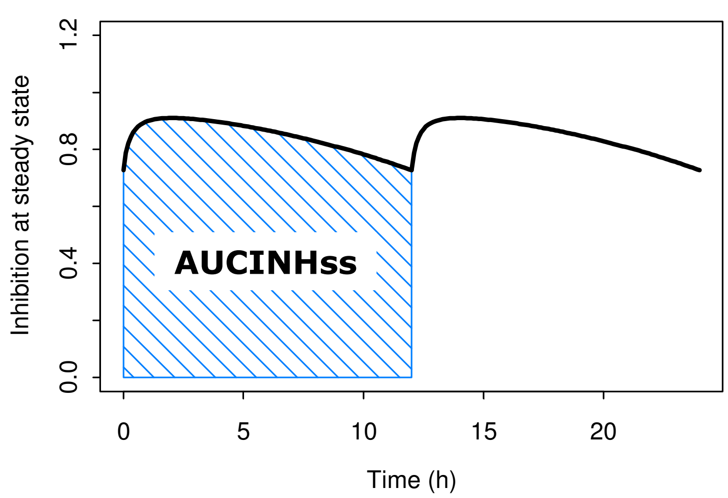
- Inhibition of proliferative systems naturally leads to binary outcomes:
  - If concentration of inhibitor (IC) > RMIC → success
  - If concentration of inhibitor (IC) < RMIC → failure
- Mechanistically, logistic regression of binary outcomes such as failure/success rates as a function of inhibitor exposure (IC) is an expression of the RMIC distribution across the population.
- Time of failure or success is a function of the IC/RMIC ratio: e.g. for failure (ratio below 1), the lower the ratio, the sooner the failure.
- Time varying inhibition of proliferative systems can be handled by calculating the equivalent effective constant concentration (ECC):

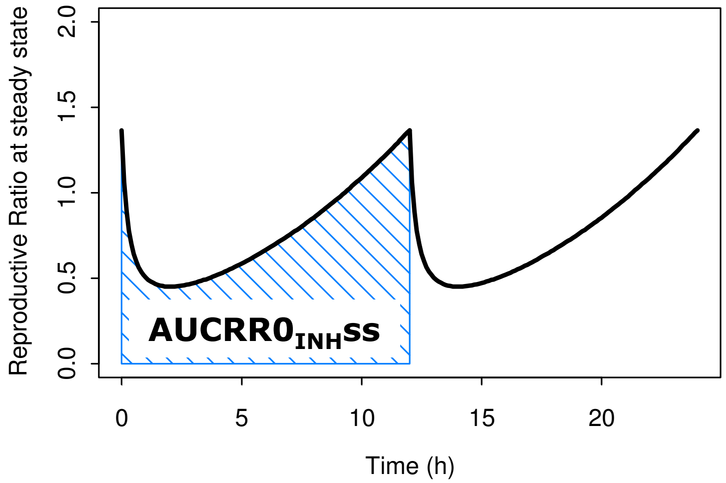
$$ECC = \frac{IC_{50} * INH_{avg}}{1 - INH_{avg}}$$

To be equally efficacious at steady state (i.e. same proliferation rate), two treatments (e.g. qd vs bid) should give rise to the same average $RR0_{INH}$

After simulations, various metrics can be calculated:







$$Css\ avg = AUCss/\tau$$

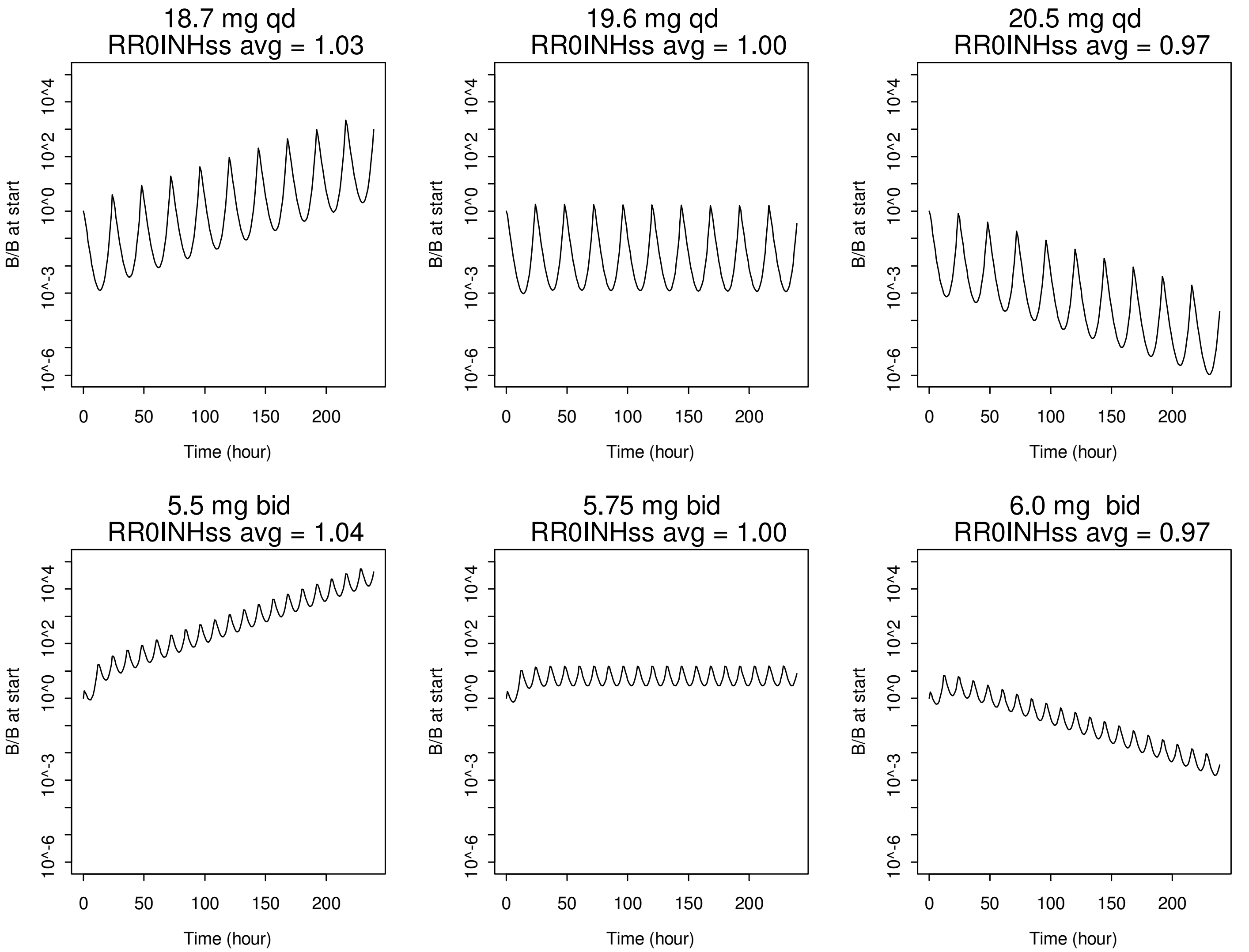
$$INHss\ avg = AUCINHss/\tau$$

$$RR0_{INH}ss\ avg = AUCRR0_{INH}ss\ /\tau$$

$$ECCss = IC_{50}*INHss\ avg/(1\text{-}INHss\ avg)$$

Whatever the dose, dosage schedule or PK parameter, scenarios that have an AVERAGE $RR0_{INH}ss=1$ lead to just survival

(Simple model)



F=1

ka=1 h^{-1}

V=70 L

ke=0.15 h^{-1}

km=5 h^{-1}

kd=1 h^{-1}

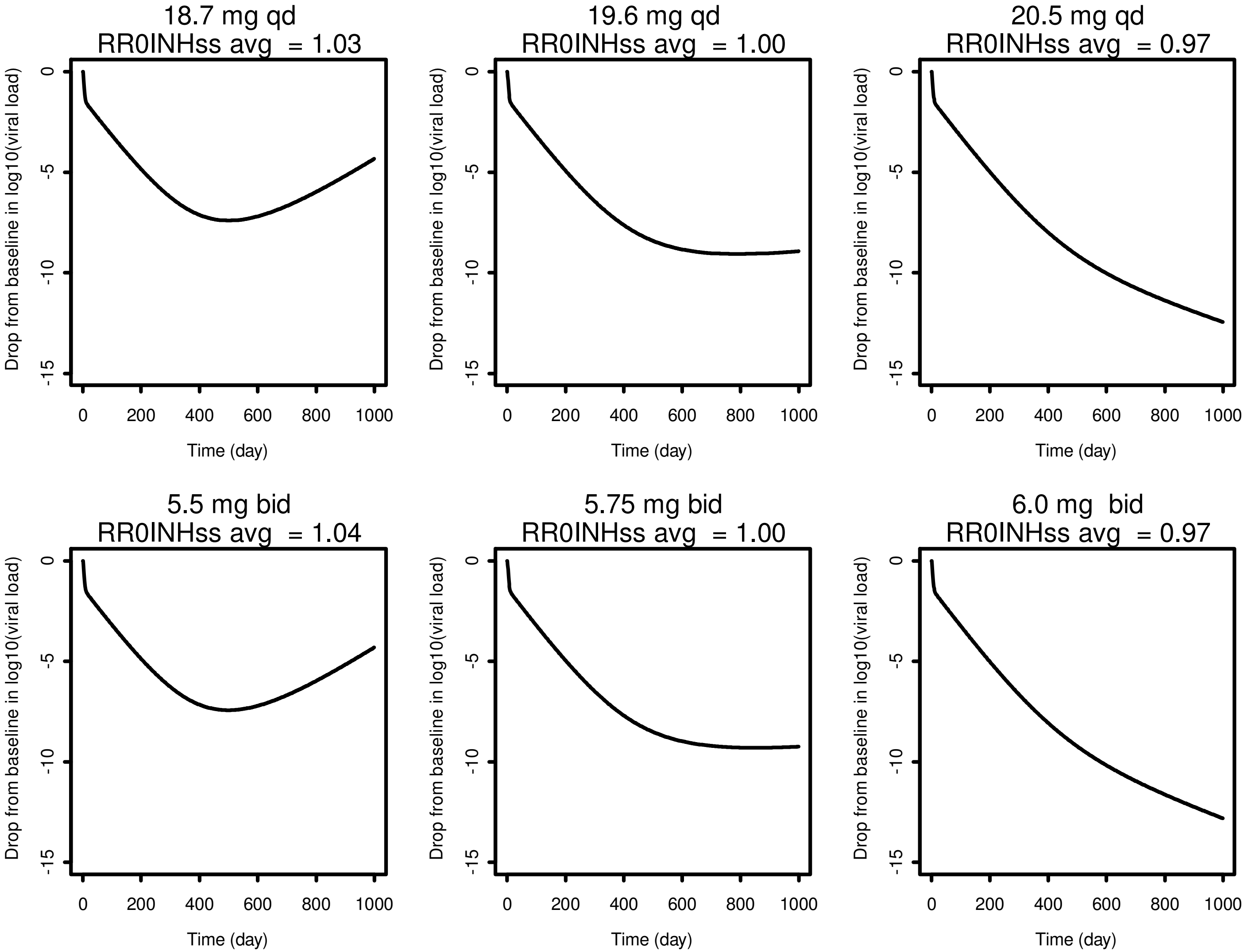
RR0=5

IC_{50}=10 ng/mL

Virtual drug

Whatever the dose, dosage schedule or PK parameter, scenarios that have an <u>AVERAGE</u> $RR0_{INH}ss=1$ lead to just survival

(Viral dynamic model)



F=1

$ka=1\ h^{-1}$

V=70 L

$ke=0.15\ h^{-1}$

RR0=5

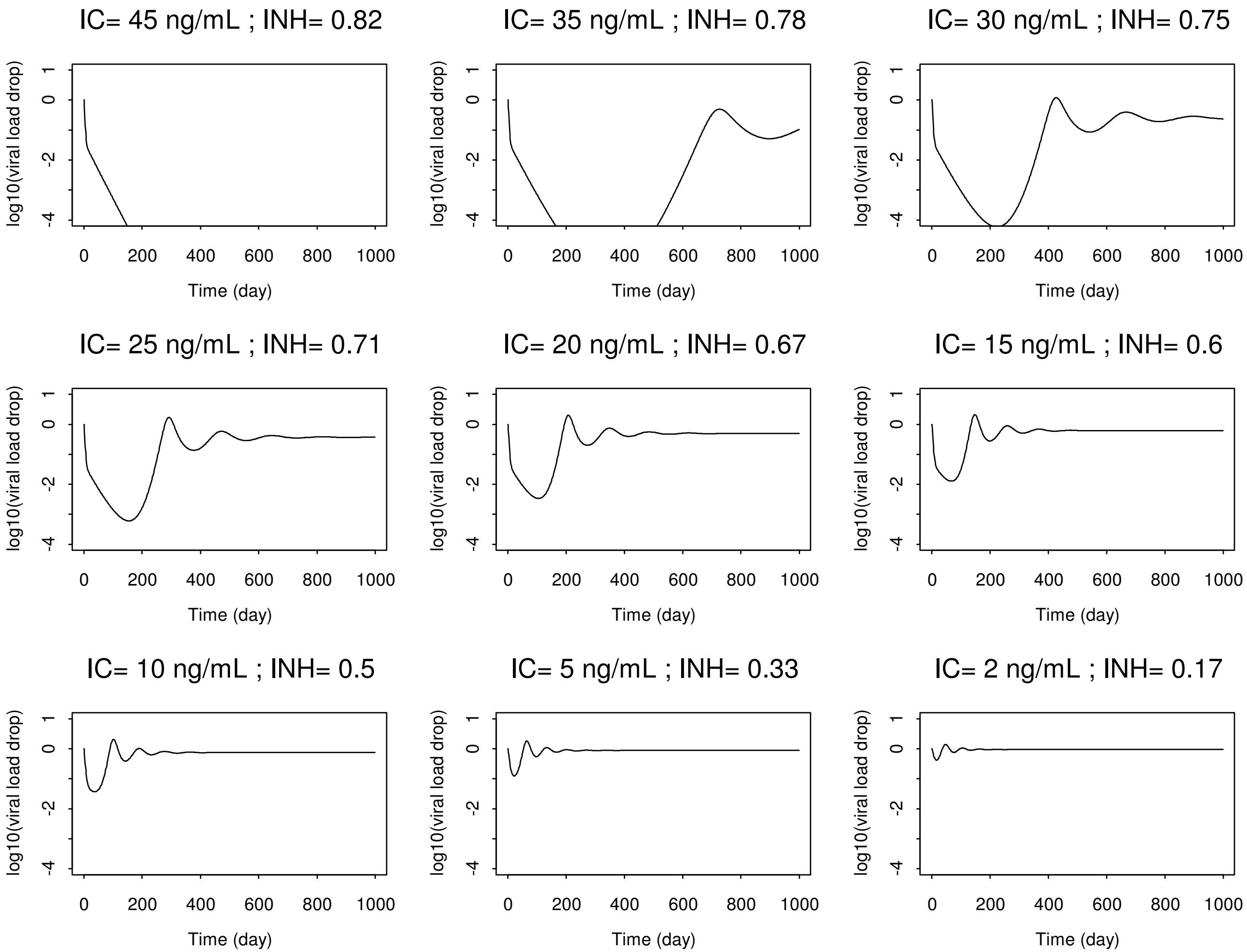
$IC_{50}=10$ ng/mL

Virtual drug

The system is characterised by a ‘breakout’ inhibition at inhibitory concentration equal to RMIC

At constant concentration less than the RMIC it is predicted that viral load will first decrease and eventually rebound…

(Drug x: RR0=5, IC50=10 ng/mL, RMIC=40 ng/mL, 'breakout' inhibition=0.8)
RMIC=(RR0-1).IC50 $RR0_{INH}$=(1-INH).RR0

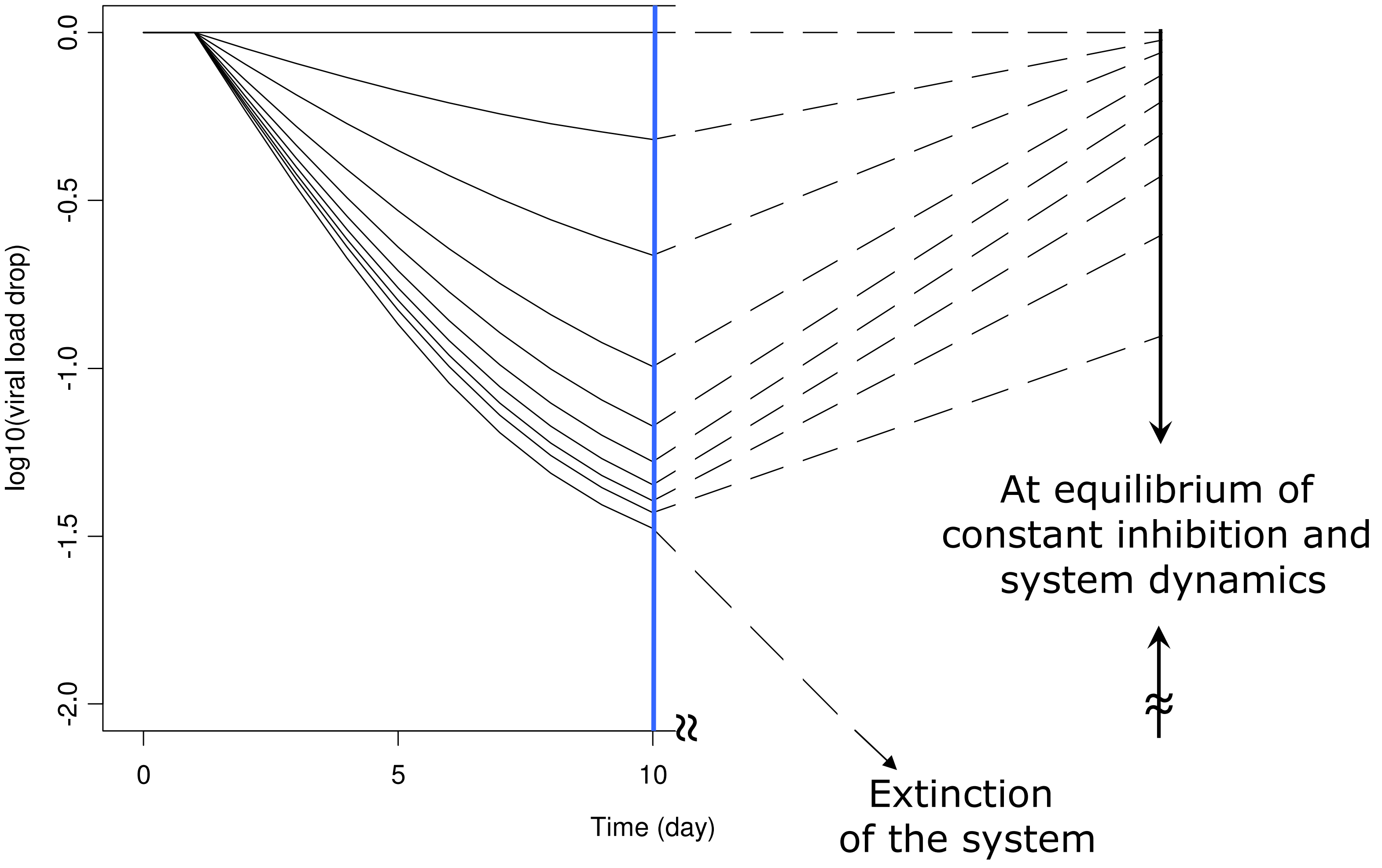


(viral dynamic model)

… rendering the initial drop of viral load not immediately predictive of the viral load at equilibrium

(Drug x: RR0=5, IC_{50}=10 ng/mL, RMIC=40 ng/mL, 'breakout' inhibition=0.8)

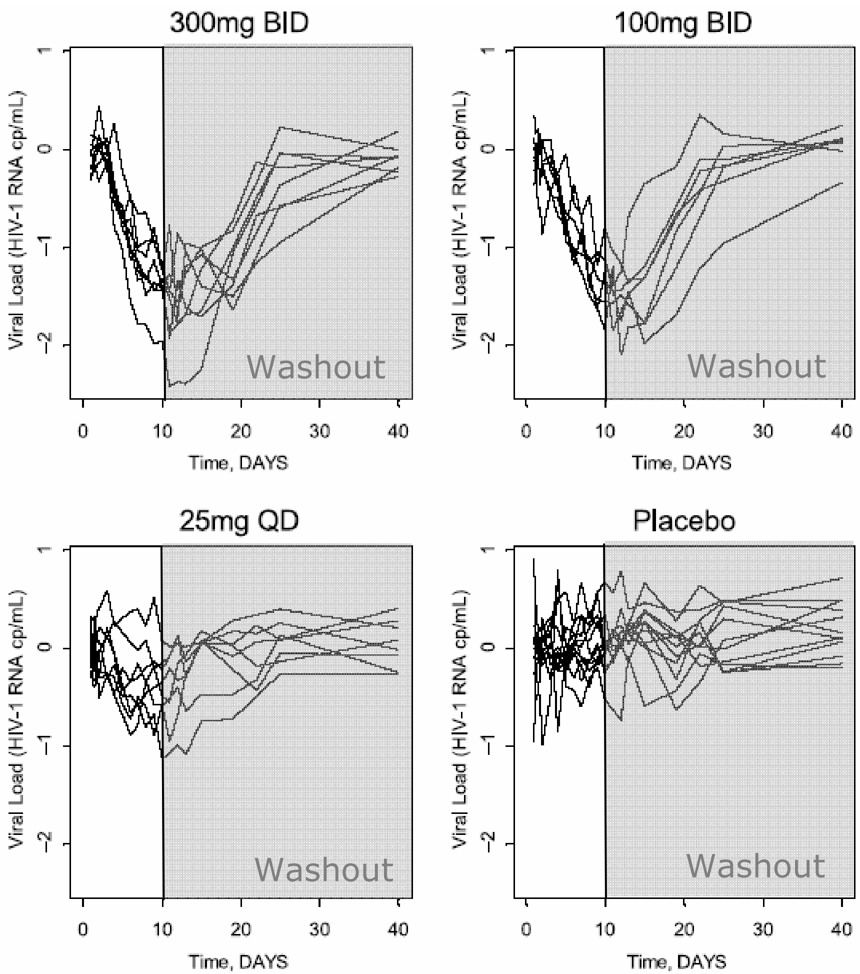
Inhibitory Concentration (IC) = 0, 2, 5, 10, 15, 20, 25, 30, 35, 45 ng/mL



(viral dynamic model)

Adequate study design and PK-PD analysis of viral load dynamics during and after short-term monotherapy can lead to the estimation of RR0 and IC_{50} (i.e. RMIC)

(Adapted from Rosario: J. Acquir. Immune Defic. Syndr. 2006,**42**:183-91)



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Infectious virus (copies HIV-1 RNA):

$DV/dt = p.A - C.V$

FIGURE 2. HIV-1 RNA $\log_{10}$ decline from baseline for the 4 treatment arms. Baseline was calculated as a mean of 3 predose viral load measurements. One patient in the 100 mg twice daily treatment arm who had a dual tropic virus at baseline was excluded from the analysis.

Inhibition of proliferative systems naturally leads to binary outcomes and logistic analysis:

If concentration of inhibitor (IC) > RMIC → success

If concentration of inhibitor (IC) < RMIC → failure

Mechanistically, logistic regression of binary outcomes such as failure/success rates as a function of inhibitor exposure (IC) is an expression of the RMIC distribution across the population

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Maraviroc Exposure Response Analysis: Phase 3 Antiviral Efficacy in Treatment-Experienced HIV+ Patients

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Conclusions

- The basic reproductive ratio (RR0) is not a new concept :
  - Ecology
  - Epidemiology
  - Biology
  - Many other areas (e.g. word survival)

- The link between PK and RR0 is rather recent (e.g. viral dynamics, ECC and RMIC).

- Starting from basic RR0-based PK-PD principles, there are many specific cases that can be explored.

- Circular models like COMA also have specific PK-PD aspects that would be interesting to investigate.