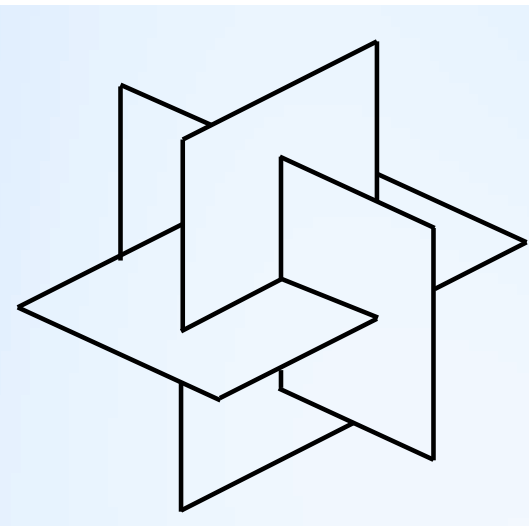




Systems Pharmacology of Chain-terminating Nucleoside Analogs

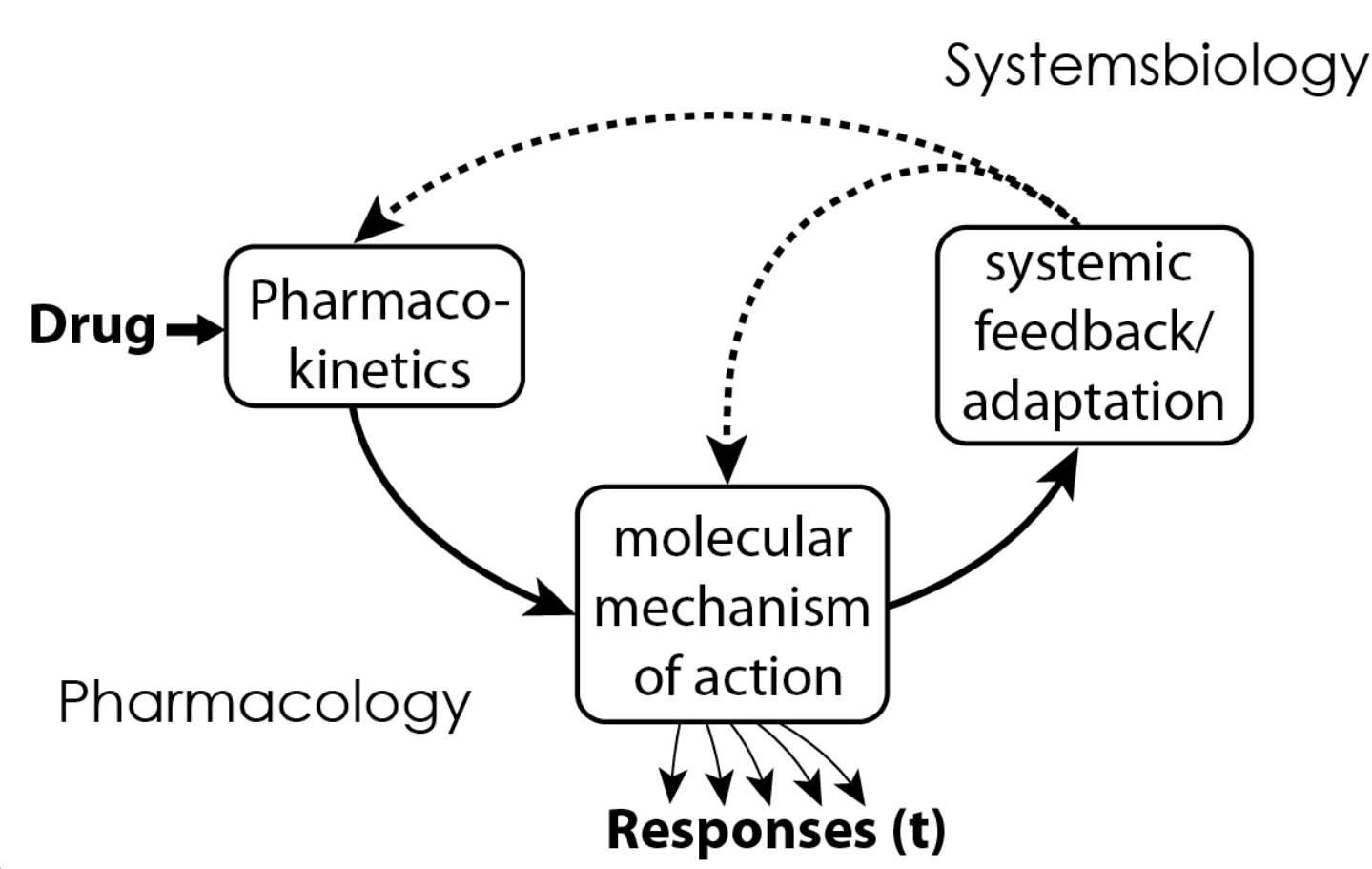


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Systems Pharmacology



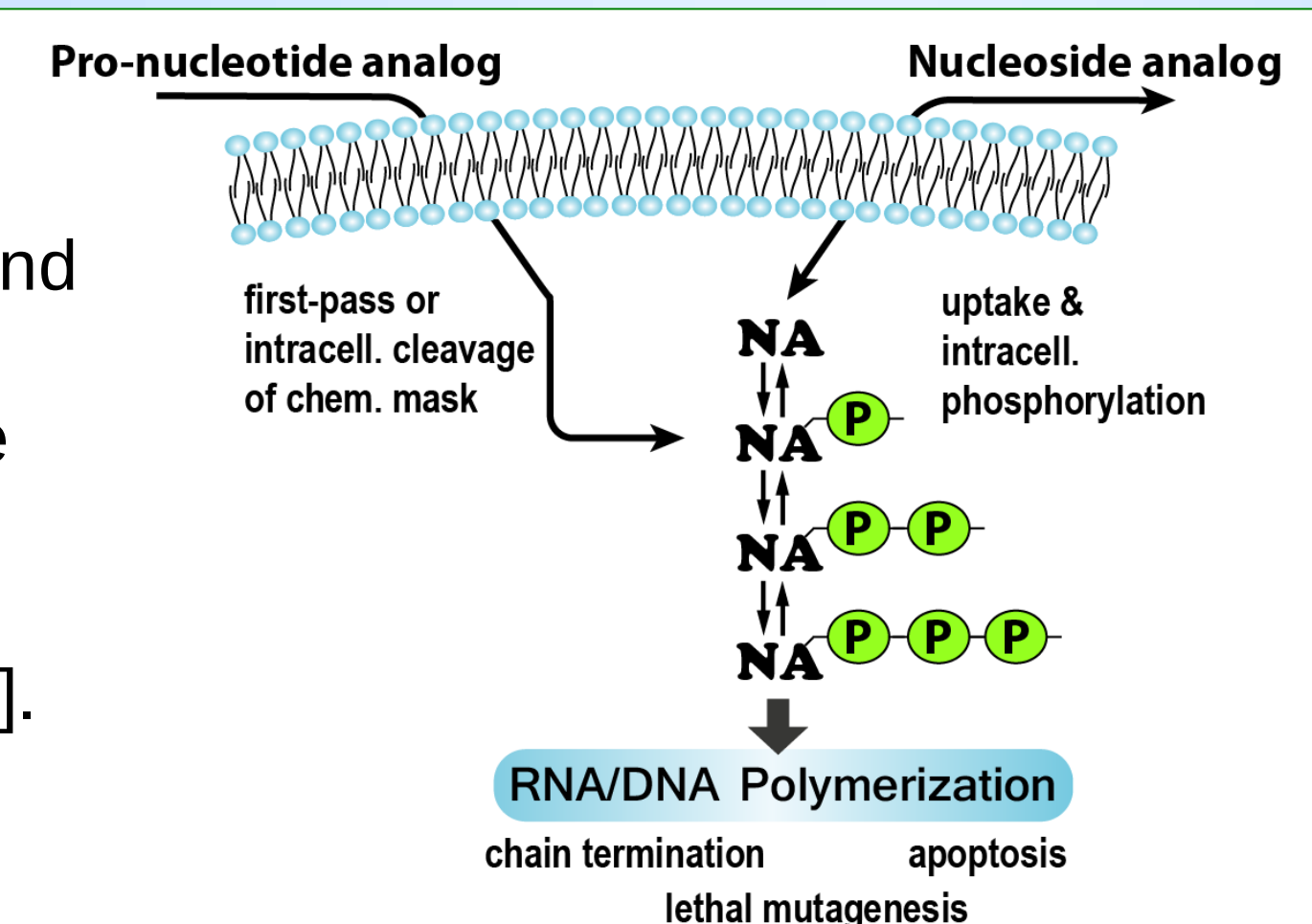
The systems biology principles [1, 2] have now been successfully applied to the level, where the phenotype of (relatively simple) organisms can be studied *in silico* based on the interactions of their inherent molecules [3]. Systems biology methods can then be utilized to identify suitable drug targets in the derived biological networks [4, 5], and appropriate drugs may be developed based on these findings. The next step is to address the implications of (time-variant) drug-interference on the biological network; the systems' feedback response and the resulting consequences for drug utility and therapy. '**Systems pharmacology**' [6] aims to take this next step, by utilizing the systems' knowledge in order to elucidate-, validate- and apply new concepts to the development- and use of drugs and to provide an integrated 'systems level' approach to determining their mechanisms of action. This unique combination of concepts from systems biology and classical pharmacology may help to gather the expertise needed to manipulate complex cellular networks in a specified way with mono- or combination therapy, so as to maximize therapeutic benefit in individual patients [6].

[1] Kitano (2002) Science 295: 1662; [2] Kitano (2002) Nature 420: 206; [3] Karr et al. (2012) Cell 150: 389; [4] Kitano (2007) Nat Rev Drug Discov 6: 202; [5] Folger et al. (2011) Mol Syst Biol 7: 501; [6] Sorger et al. (2011) NIH white paper by the QSP workshop group

Nucleoside Analogs

Nucleoside analogs (NAs) are an important drug class for the treatment of viral infections (e.g. HBV, HCV, HSV and HIV) and cancer [1]. They are administered as pro-drugs, which, after intracellular activation/phosphorylation, compete with their respective natural nucleotide counterpart (dNTP/NTP) for incorporation into nascent DNA or RNA. Incorporated NAs cause subsequent chain termination, induce lethal mutagenesis or cause DNA damage, which may induce apoptosis. Target-site concentrations depend on the abundance of cellular transporters, -kinases and -phosphatases. Pharmacology and toxicodynamics on the other hand are affected by the (cell-specific) abundance of endogenous polymerase substrates [2,3].

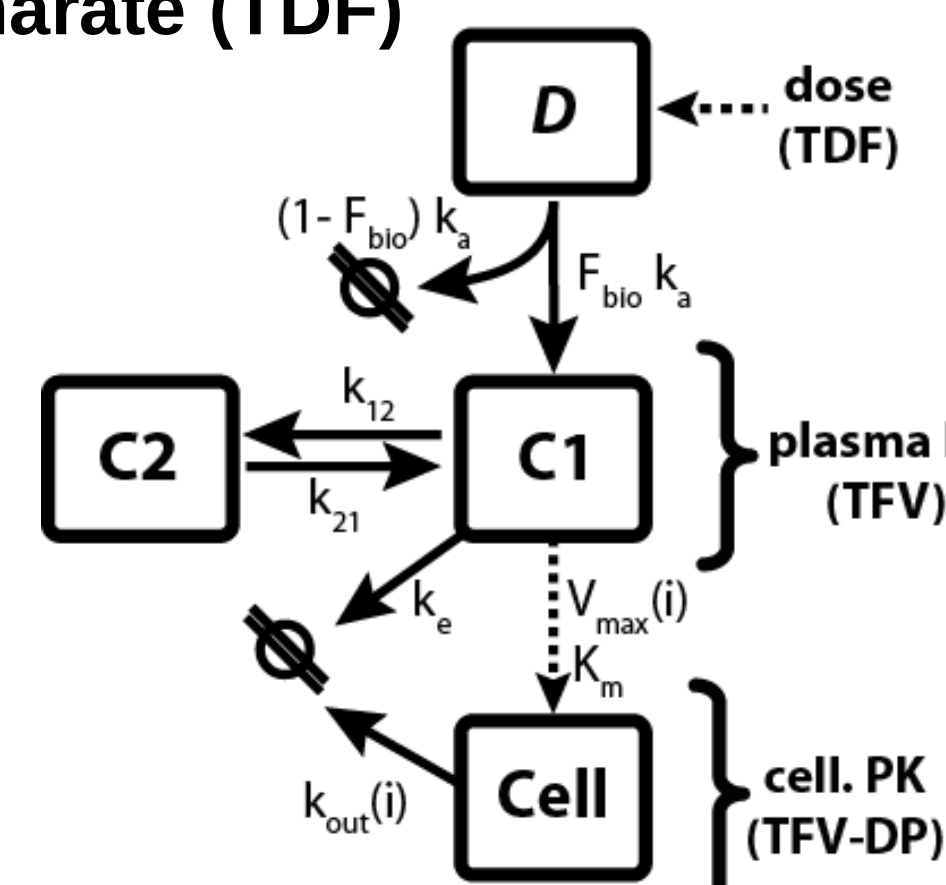
[1] Jordheim Nat Rev Drug Discovery (2013)12: 447; [2] Cheng & Prusoff.Biochem Pharm (1973) 22: 3099; [3] Swinney (2004) Nat Rev Drug Discovery (2004) 3: 801



1. Pharmacokinetics

Most NAs are administered as inactive nucleosides, or pro-nucleotide analogs. They undergo cellular uptake and subsequent phosphorylation to exert their effect. (Prodrug) plasma pharmacokinetics and effect-site pharmacokinetics of the active anabolites are often asynchronous and cell-specific. In order to predict NA pharmacodynamics it is therefore of utmost importance to characterize the dynamic relationship between prodrug dosing and intracellular levels of active NA anabolites.

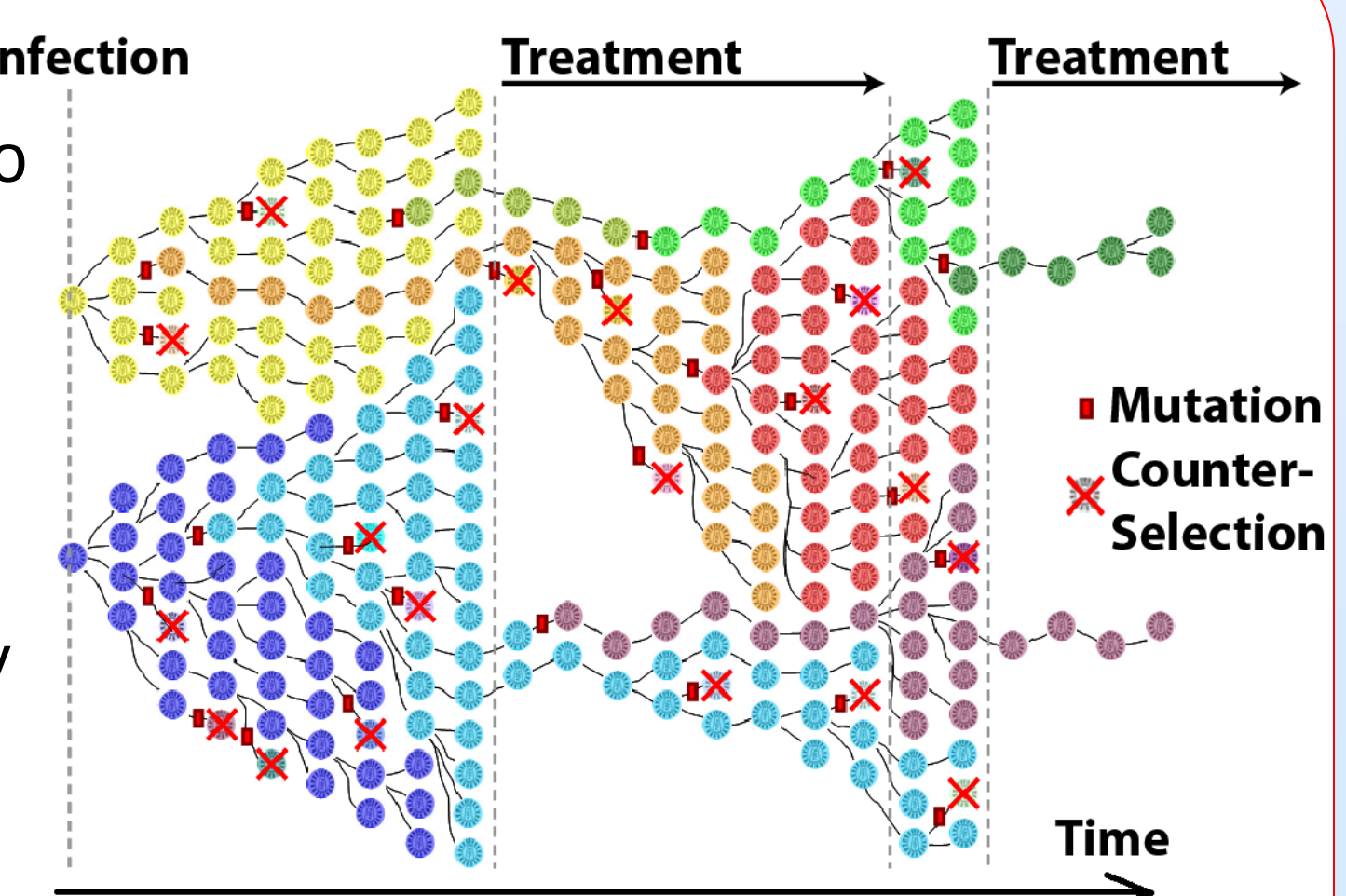
Example: Tenofovir disoproxil fumarate (TDF)



Further Reading: Duwal et al. PLoS One (2012) 8, e40382; von Kleist et al. Eur J Pharm Sci (2009) 36, 532

3. Adaptation

Viruses (and cancer) can adapt to treatment induced stress by e.g. acquiring resistance mutations. However, their ability to evolve depends on the availability of admissible "escape pathways". These pathways are restricted by genetic distance, epistasis and drug pressure itself.



Further Reading: von Kleist et al. PLoS Comput. Biol. (2010) 6, e1000720; von Kleist et al. PLoS One (2011) 6, e18204; Frank et al. (2011) Antimicrob Agents Chemother. 55, 5529; Rath et al. PLoS One (2013) 8, e61102

2. Molecular Mechanisms of Action (MMOA)

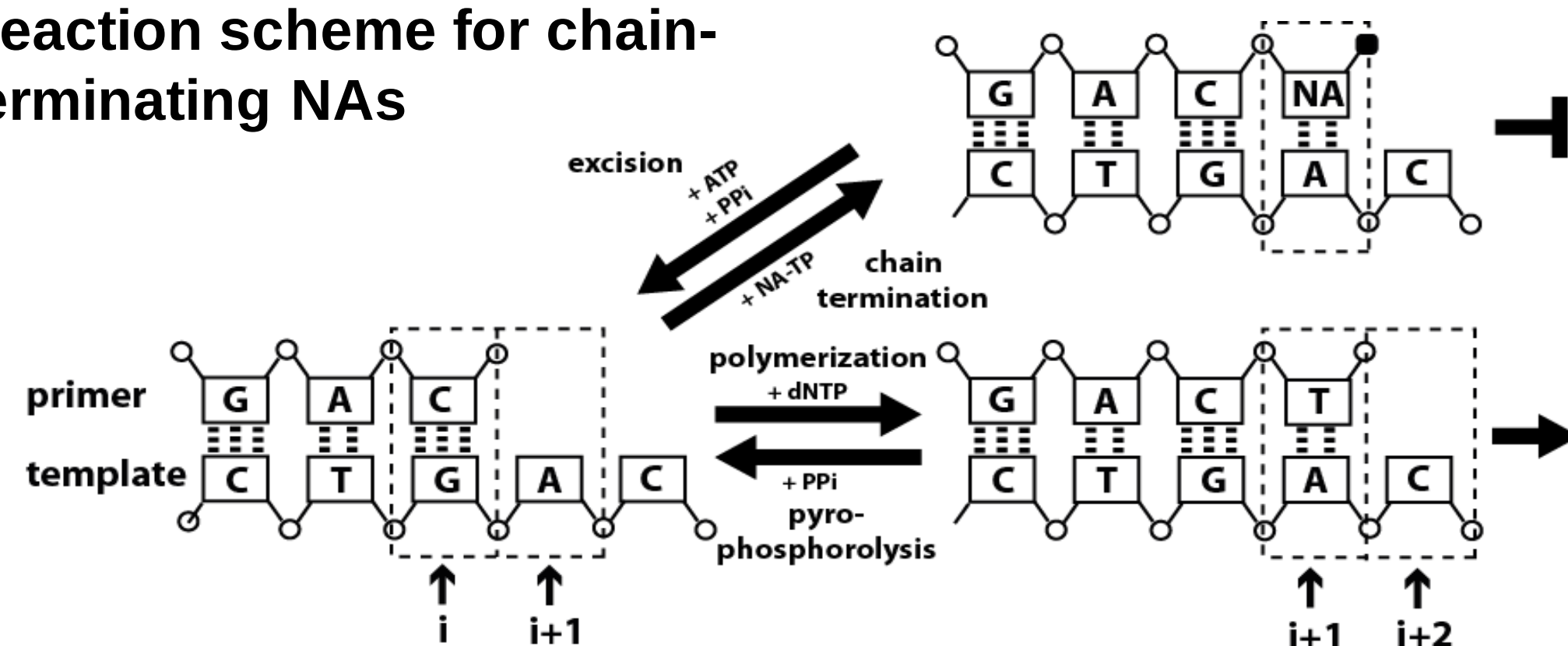
Based on the reaction scheme below, we formulated the underlying dose-response relation for chain-terminating NAs in terms of a mean first-hitting-time model, which could be solved analytically to derive a mechanistic expression for the IC₅₀ value, revealing kinetic, as well as cell-specific parameters of drug efficacy.

Further Reading: von Kleist et al. PLoS Comput. Biol. (2012) 8: e1002359

$$\eta(\text{NA, wt}) = \frac{T_{0 \rightarrow N}(\phi, \text{wt})}{T_{0 \rightarrow N}(\text{NA, wt})} \quad T_{0 \rightarrow N} = \sum_{i=0}^{N-1} T_{i \rightarrow i+1}$$

$$T_{i \rightarrow i+1} = \left(\tau_{i+1} \cdot \rho_{i \rightarrow i+1} + \tau_i + \rho_{i \rightarrow i-1} T_{i-1 \rightarrow i} \right) \frac{1}{\rho_{i \rightarrow i+1}}$$

Reaction scheme for chain-terminating NAs

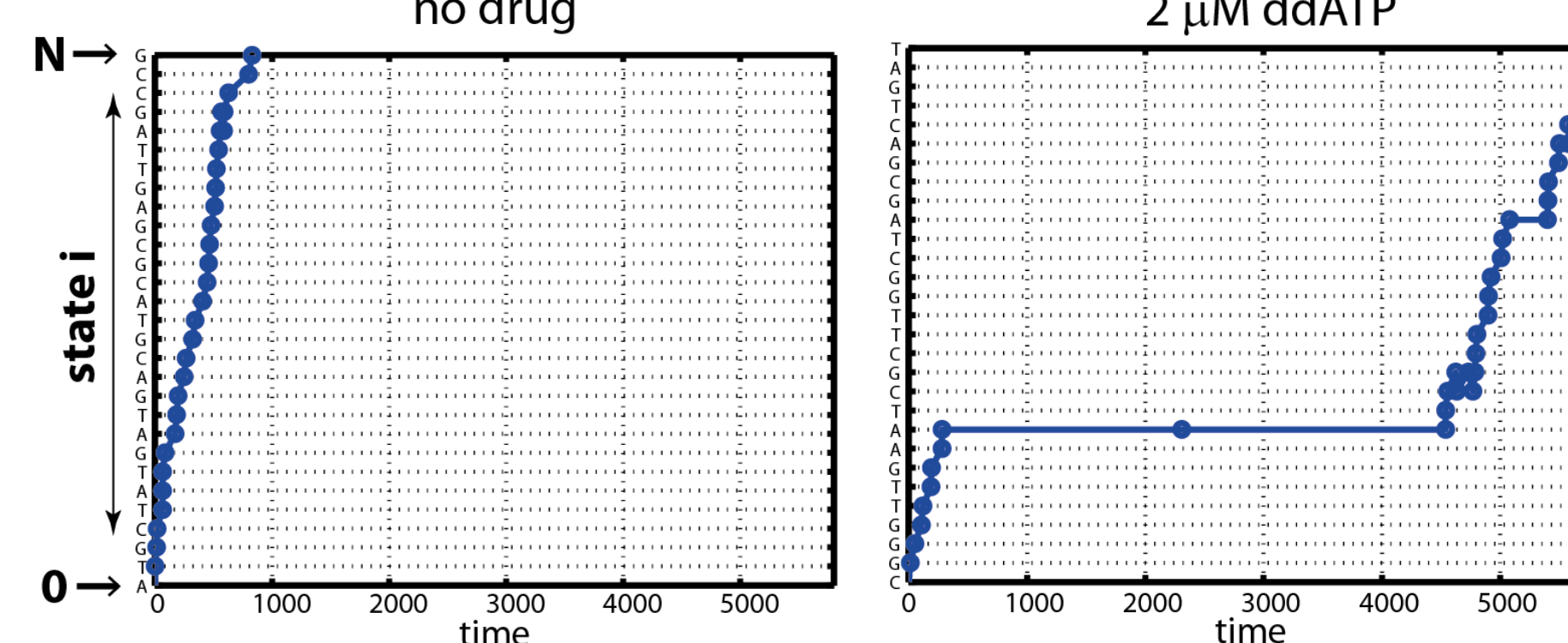


$$\text{IC}_{50} \approx \frac{r_{\text{exc}}}{k_{\text{term}} + r_{\text{exc}}} \cdot K_{D, \text{NA}} \left(1 + \frac{[\text{dNTP}]}{K_{D, \text{dNTP}}} \right)$$

Hitting times (= time required to form the polymerase product)

Below, left: Time required (x-axis) to form DNA strand (depicted on the y-axis)

Below, right: Inhibitor introduces „waiting states“ after incorporation by (quasi-)terminating the nascent DNA strand.

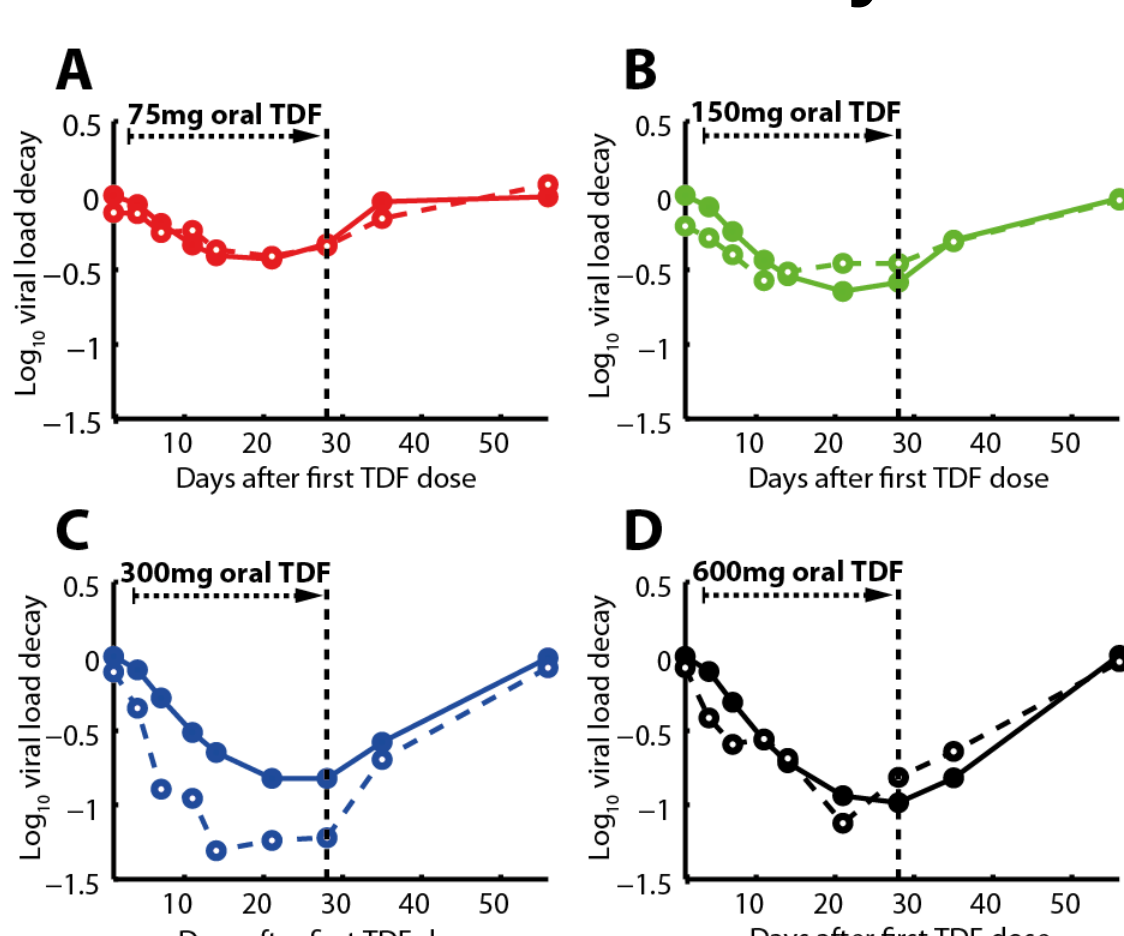


4. Drug response

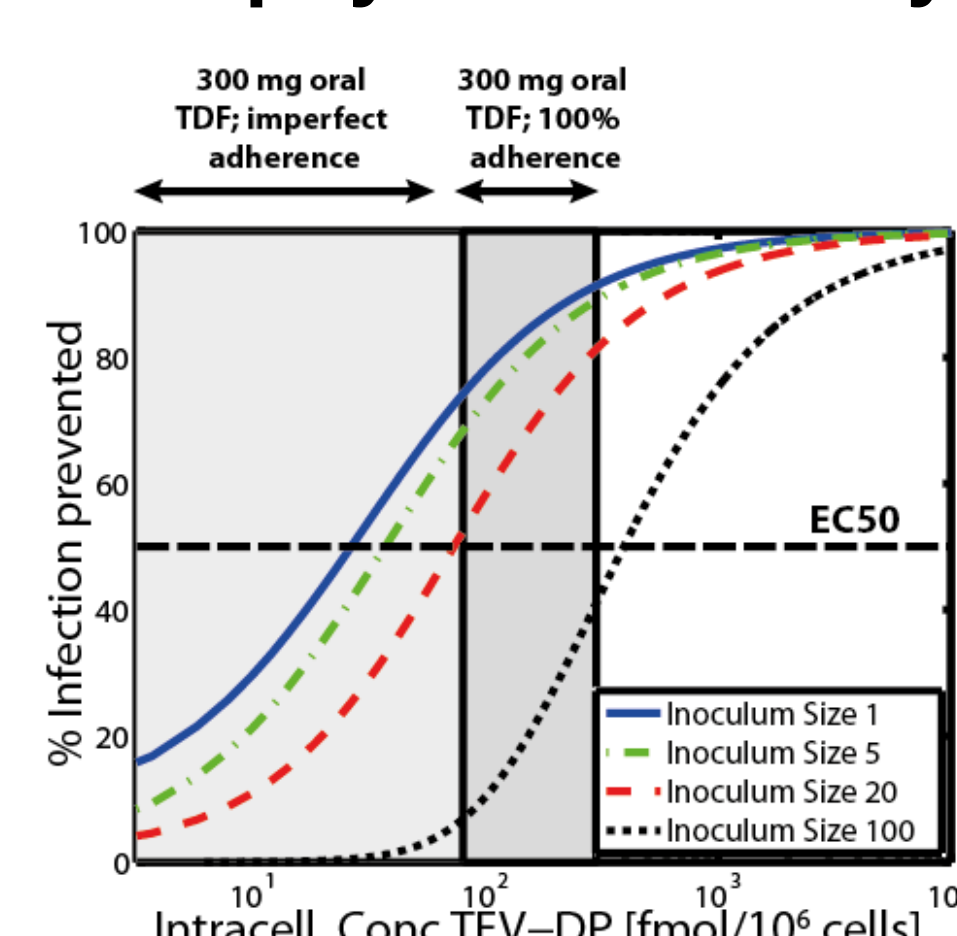
Example: Tenofovir disoproxil fumarate (TDF)

Further Reading: Duwal et al. PLoS One (2012) 8, e40382

Antiviral efficacy



Prophylactic efficacy



Conclusions

The presented approach allows combining bottom-up and top-down approaches to quantify and elucidate mechanisms of NA drug efficacy. This allows for a more complete picture of drug-interference on the molecular-, cellular- and whole body level that can be very useful for drug design and optimal therapy.