

Impact of randomness of mutation dynamics on the development of drug resistance under antiviral therapy

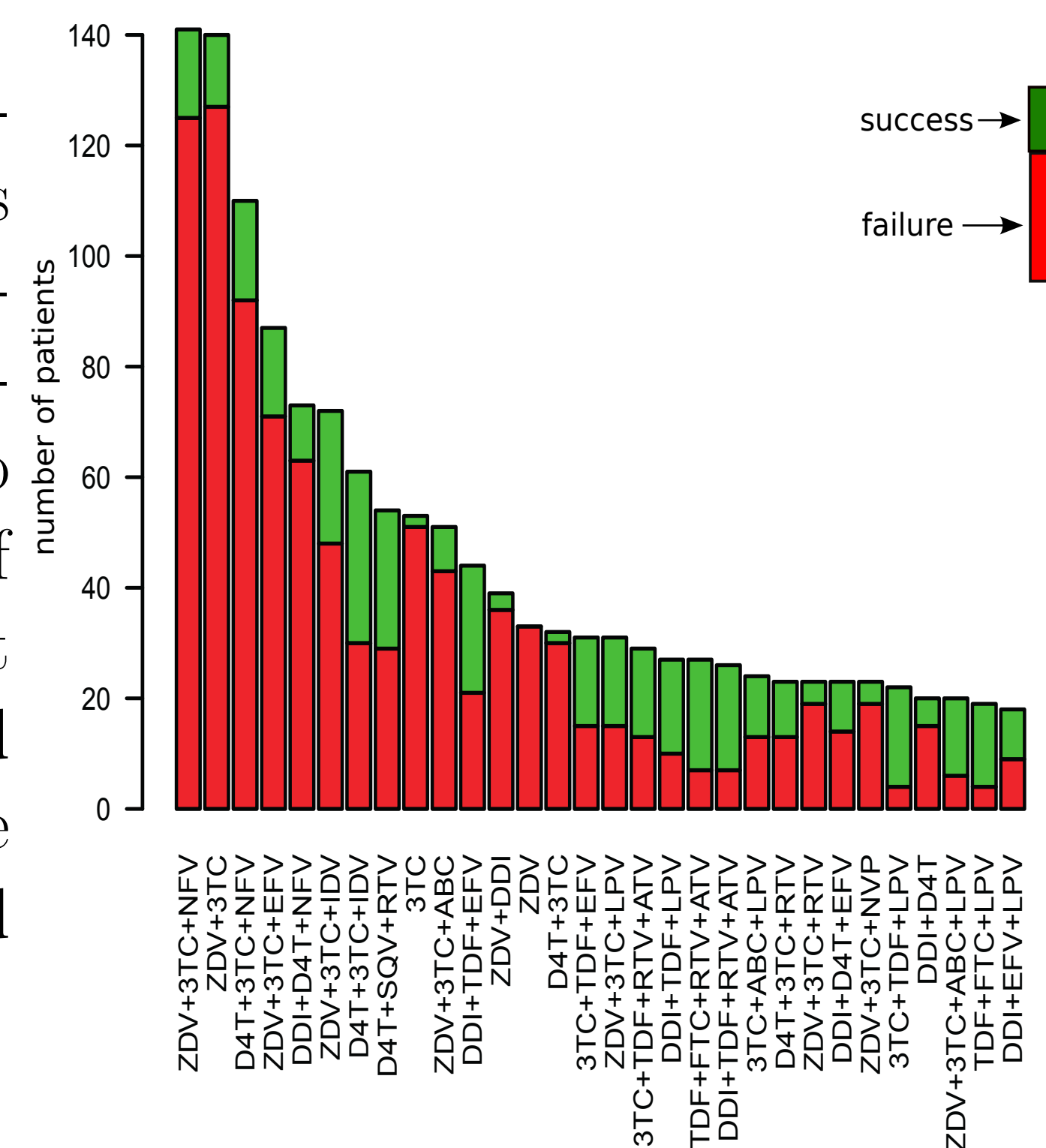
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Motivation

Observed randomness of treatment outcome

The emergence of resistant mutations within treated HIV patients has been intensively studied by deterministic mathematical models [2]. These models, however, are not able to predict the observed probability of treatment success/failure in patient data (see figure on the right based on the Swiss Cohort Study Database [1]). Successful treatment is defined as viral load below 400 c_{ps}/ml.

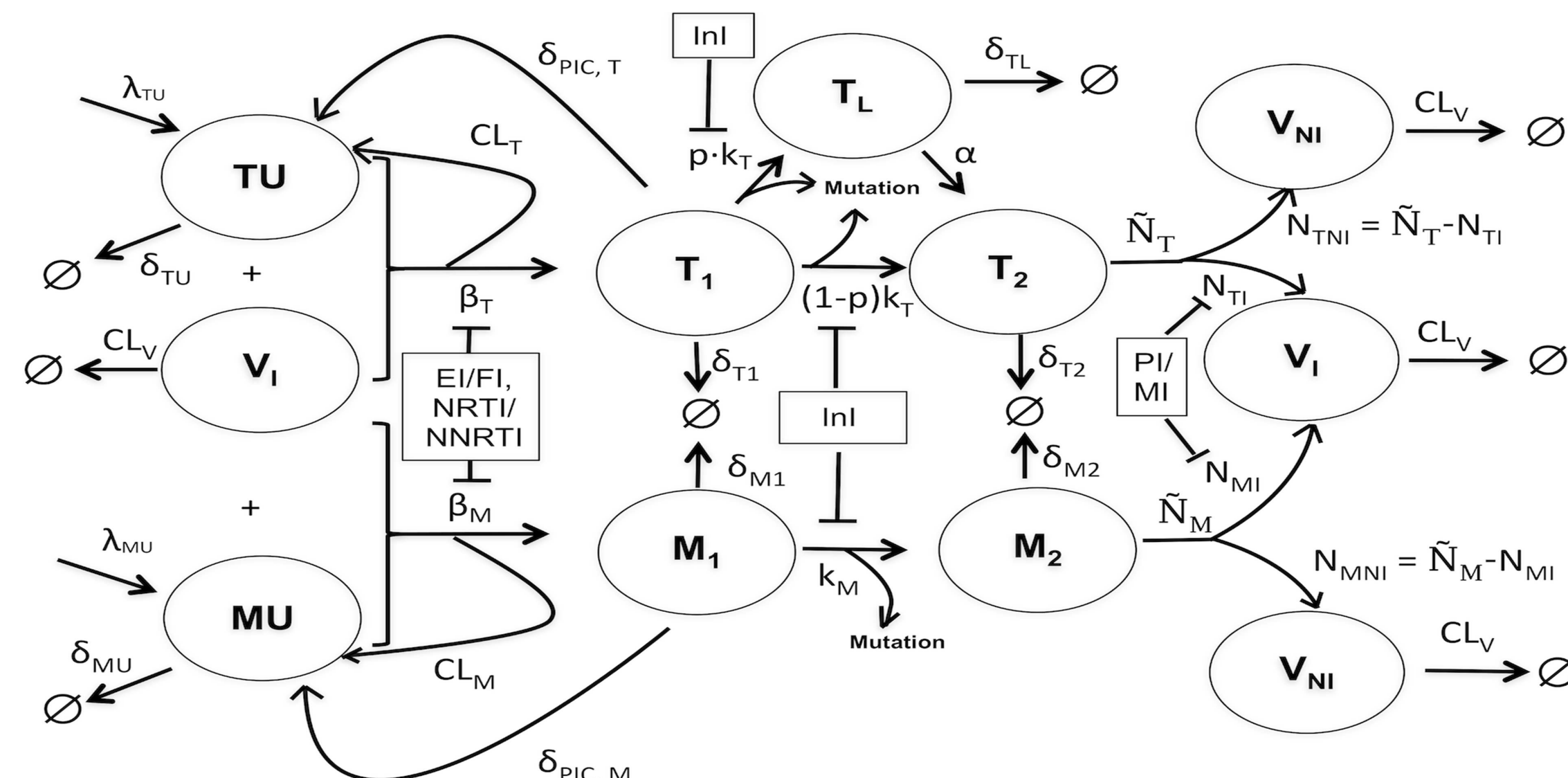


Objective: Quantification of the impact of random effects on the resistance and treatment outcome

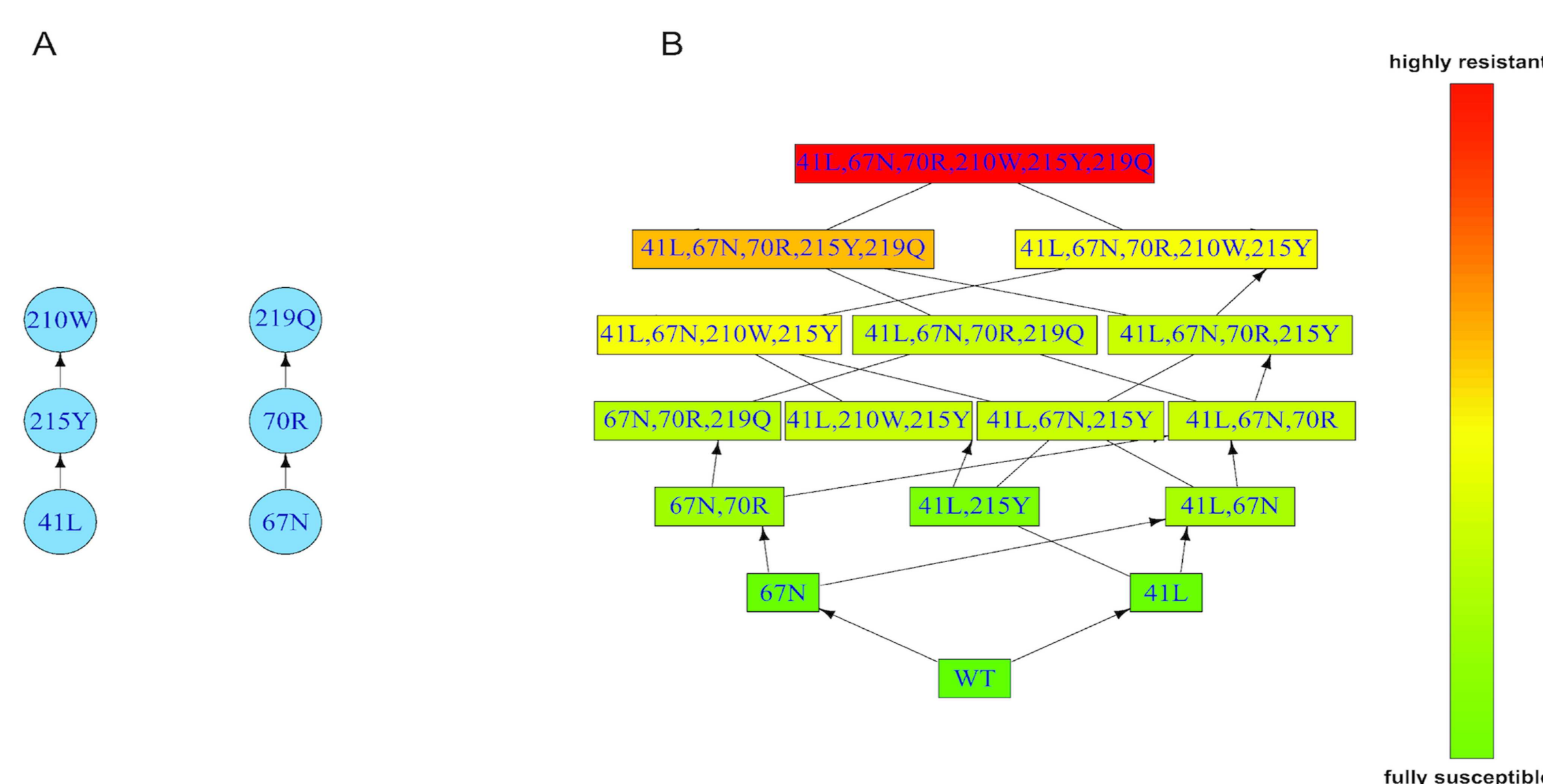
Methods

Viral dynamics and mutation model

We used a validated two-stage model for the viral dynamics [2] (see figure below). This model includes fitness costs (s_g) and resistant factors (RF_g) of different mutant genotypes, which were estimated from clinical data.



To illustrate the impact of randomness on the resistance, two different HIV mono-therapies were considered: zidovudine (ZDV) and indinavir (IDV). For both realistic mutation schemes have been inferred by statistical models [2]. For ZDV the poset and genotype lattice is given in the figure below.



Hybrid stochastic-deterministic model

The stochastic model was implemented based on a hybrid approach [3]. In this approach elementary reactions are modelled as discrete stochastic events if their propensity function a_j is below a threshold. All other reactions are modelled deterministically.

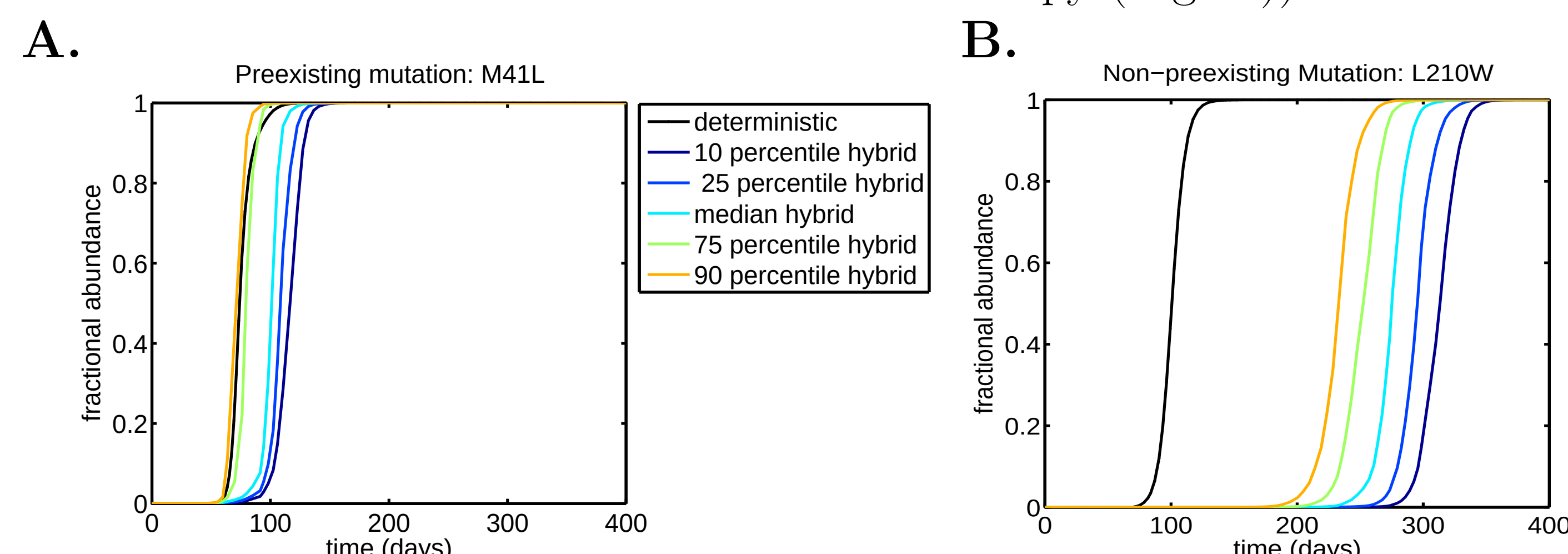
$$dX(t) = \sum_{j \in \mathcal{S}} \nu_j d\xi_j(t) + \sum_{j \in \mathcal{D}} \nu_j a_j(X(t)) dt$$

Results

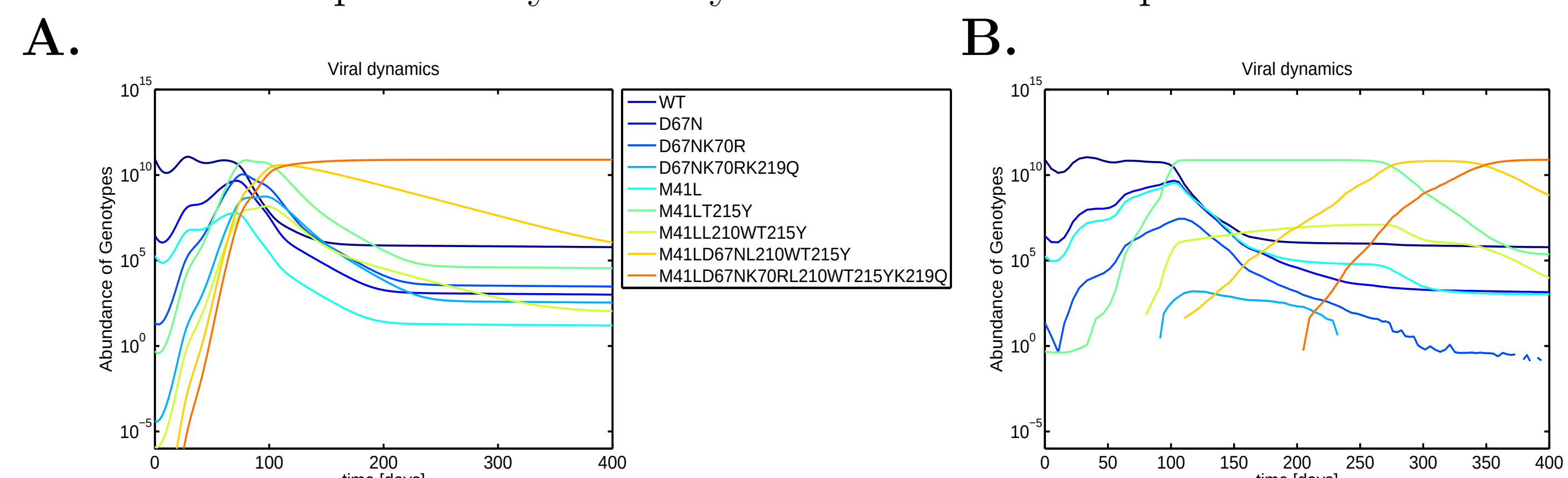
Impact of randomness on appearance of mutations

We observed that the accumulation dynamics of mutations differ between the two modelling approaches. Furthermore the appearance of mutations is delayed in the stochastic model.

- some mutations have a transient rise, not present in the deterministic model (e.g for A71V a mutation observed under IDV therapy (not shown)).
- small delay for preexisting genotypes (e.g. M41L a mutation observed under ZDV therapy (Fig. A))
- up to more than twofold delay for non-preexisting genotypes (e.g. L201W a mutation observed under ZDV therapy (Fig. B))



This can be explained by the way the viral load is represented.



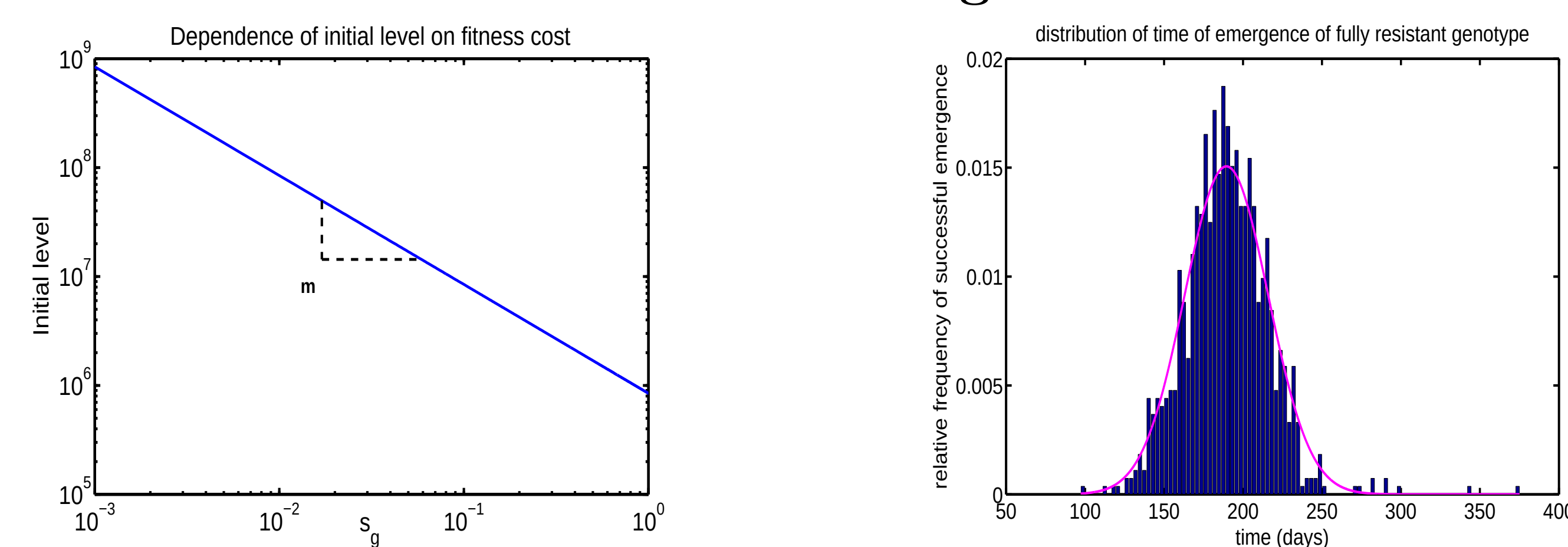
Deterministic:

- approximates viral numbers continuously
- all genotypes instantaneously present

Stochastic:

- accounts for discreteness of viral numbers
- randomness of mutation events

Initial levels and distribution of emergence of mutations



- simplified model with one mutation by varying fitness cost
- Initial level = $\text{Const} \cdot s_g^{-m}$ with $m=1.003$ (nonlinear relationship)
- simplified model with three mutations in series by varying fitness cost of last genotype
- fitness cost of preceding genotypes impact emergence of a genotype

These results and the possibility of the stochastic model to predict distributions (see figure above) will enable us to provide a more realistic description of the emergence of drug resistance.

Conclusion

Randomness and discreteness of viral load impact the emergence of mutations. This is expected to have a major impact on the mutation dynamics under combination therapy.

Literature

- [1] N. Beerenwinkel, H. Montazeri, H. Schuhmacher, P. Knapfer, and Y. et al. von Wyl. The individualized Genetic Barrier Predicts Treatment Response in a Large Cohort of HIV-1 Infected Patients. *PLoS Comput Biol* 9, 8, 2013.
[2] S. Gopalakrishnan, H. Montazeri, S. Menz, N. Beerenwinkel, and W. Huisinga. Estimating HIV-1 Fitness Characteristics from Cross-Sectional Genotype Data. *PLoS Comput Biol* 10, 11, 2014.
[3] M. von Kleist, S. Menz, H. Stocker, K. Arasteh, C. Schütte, and W. Huisinga. HIV Quasispecies Dynamics during Pro-Active Treatment Switching: Impact on Multi-Drug Resistance and Resistance Archiving in Latent Reservoirs. *PLoS One* 6, 3, 2011.