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Objective

The failure of protease inhibitor containing anti-HIV drug regimens without the detection of protease-resistant mutations (Figure 1) poses a puzzling biological and clinical dilemma [1]. Mathematical models of viral dynamics and mutations have aided in understanding causes of therapy failure with single drugs. However, parameter estimation in such complex nonlinear models has inherent challenges [2].

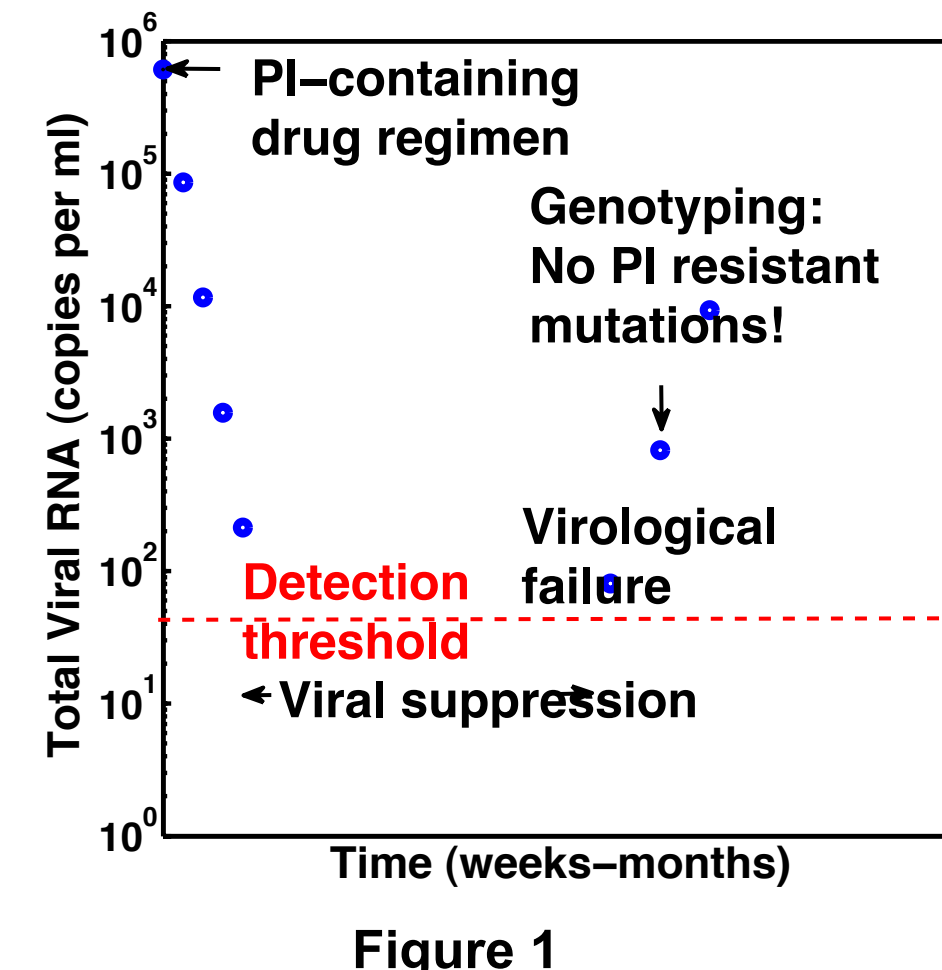


Figure 1

The objectives here were:

- to demonstrate the benefit of regularization techniques developed for linear systems, in stabilizing parameter estimation for our nonlinear viral dynamics model, and
- to assess genotypic reasons for therapy failure with multi-drug regimens and to determine how the efficacy of each drug in a combination-regimen individually affects treatment outcome

Methods

Multiple drug therapy:

To capture the dynamics of different mutant genotypes, we used a validated viral dynamics model [3] (Figure 2). Continuous-time conjunctive Bayesian network models that learn orders of mutations and the relative waiting times to their occurrence from clinical data, were utilized to model mutation accumulation [4]. We estimated fitness costs and resistance factors of different mutant genotypes by simulated annealing (see our poster at PAGE 2013 [5] for details)

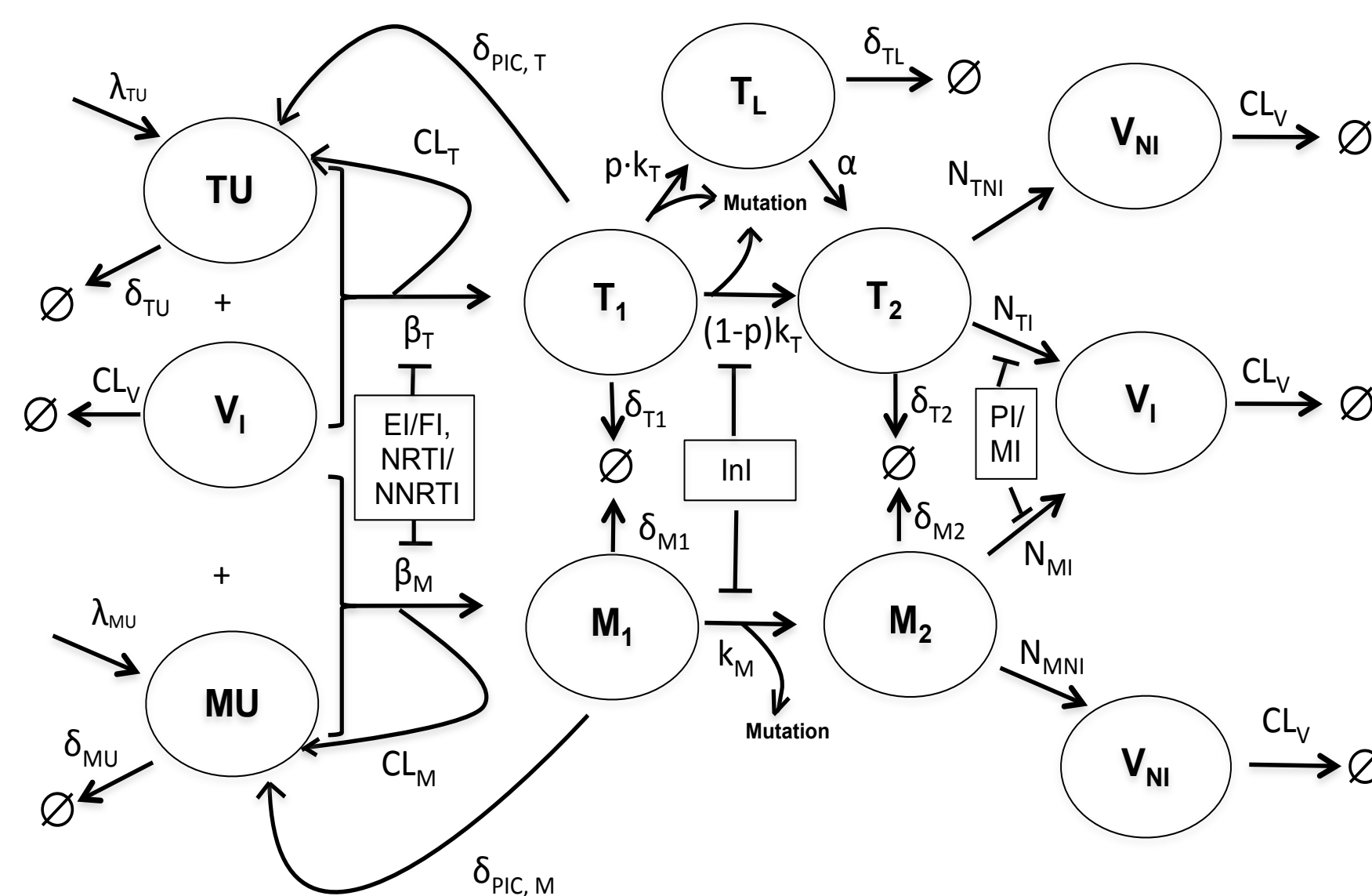


Figure 2

We illustrated our approach using a dual therapy of zidovudine (ZDV) and indinavir (IDV), two standard anti-HIV drugs. The drug-efficacies, resistance factors and fitness costs of mutations could readily be incorporated in the mechanistic model. For the mutations, we defined the combined poset of mutations as the disjoint union of the individual posets (Figure 3).

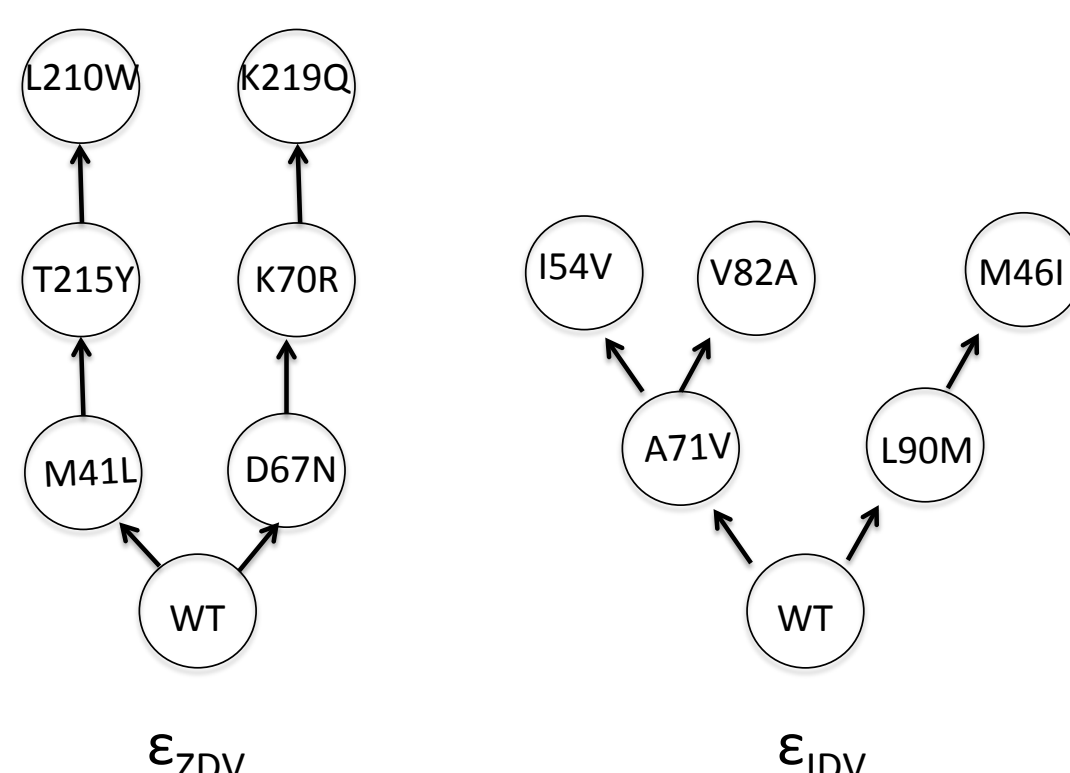


Figure 3

Regularization:

To study the impact of regularization on parameter estimation, we used ridge regression – a statistical inference technique commonly used in linear regression [6]. Briefly, if $Y = f(X, \beta)$ is a linear model and data (X, Y) are given in order to estimate β , then the minimization problem in ridge regression can be formulated as

$$\beta = \arg \min_{\beta} \sum (Y - f(X, \beta))^2 + \lambda \cdot \sum |\beta|^2$$

We explored the application of ridge regression in estimating fitness costs of ZDV mutant genotypes.

Results

Dual therapy

Our simulations enabled us to predict the dominant mutant genotypes at the point of failure. We observed that there are different regimes of the individual drug efficacies that result in varying causes of failure (Figure 4A). With usual efficacies of 0.75 and 0.90 for ZDV and IDV respectively (see [5] for details), for example, we noted virological failure after ~3 months (Figure 4B) due to mutations resistant to both drugs. In this case, the wild type was sufficiently suppressed and monotonically declined during the treatment period.

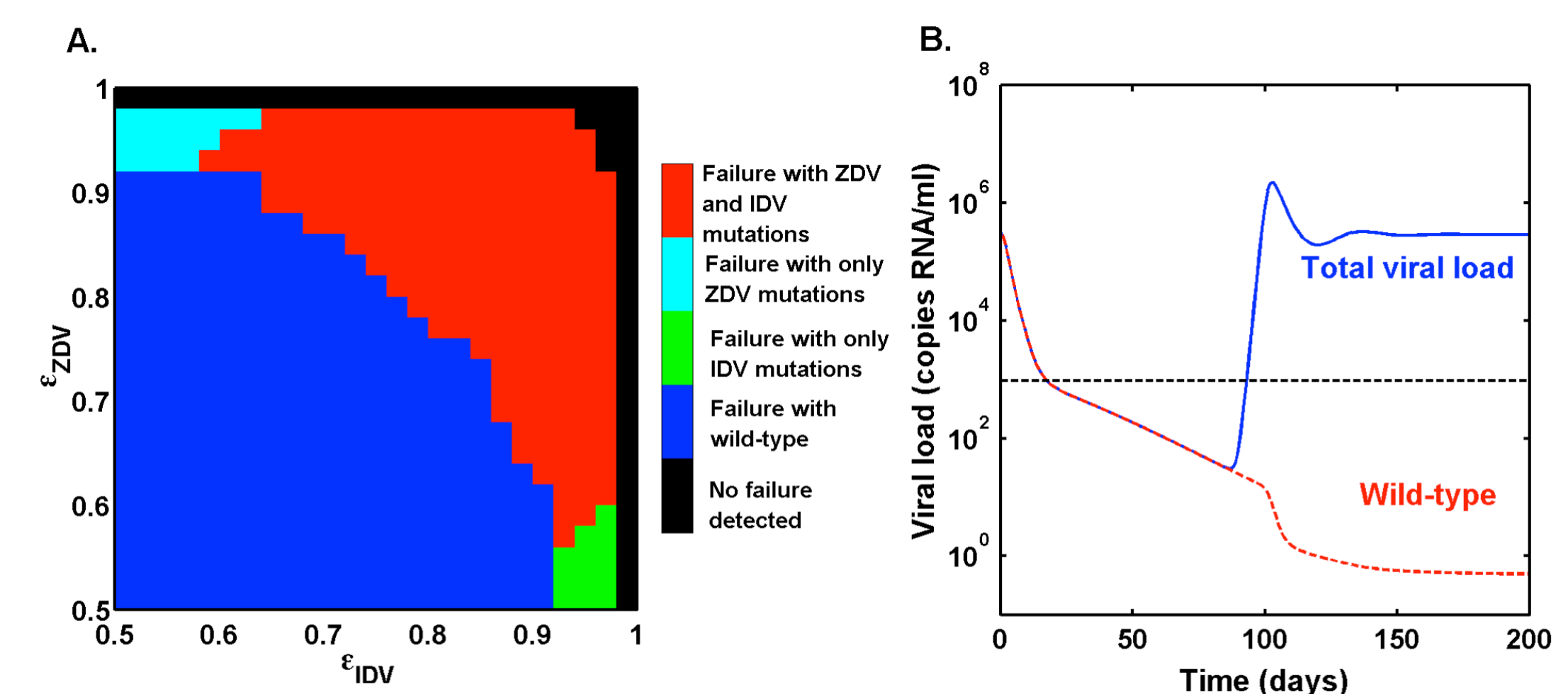


Figure 4

However, we identified combinations of drug efficacies, where treatment failure occurred due to insufficient suppression of the wild type. This could indicate insufficient drug pharmacokinetics, a low drug efficacy or poor adherence, with implications in designing a salvage therapy regimen, subsequent to failure. Interestingly, we also observed that there are combinations of drug efficacies, for which failure occurs due to mutations to only one of the two drugs (Figure 4A).

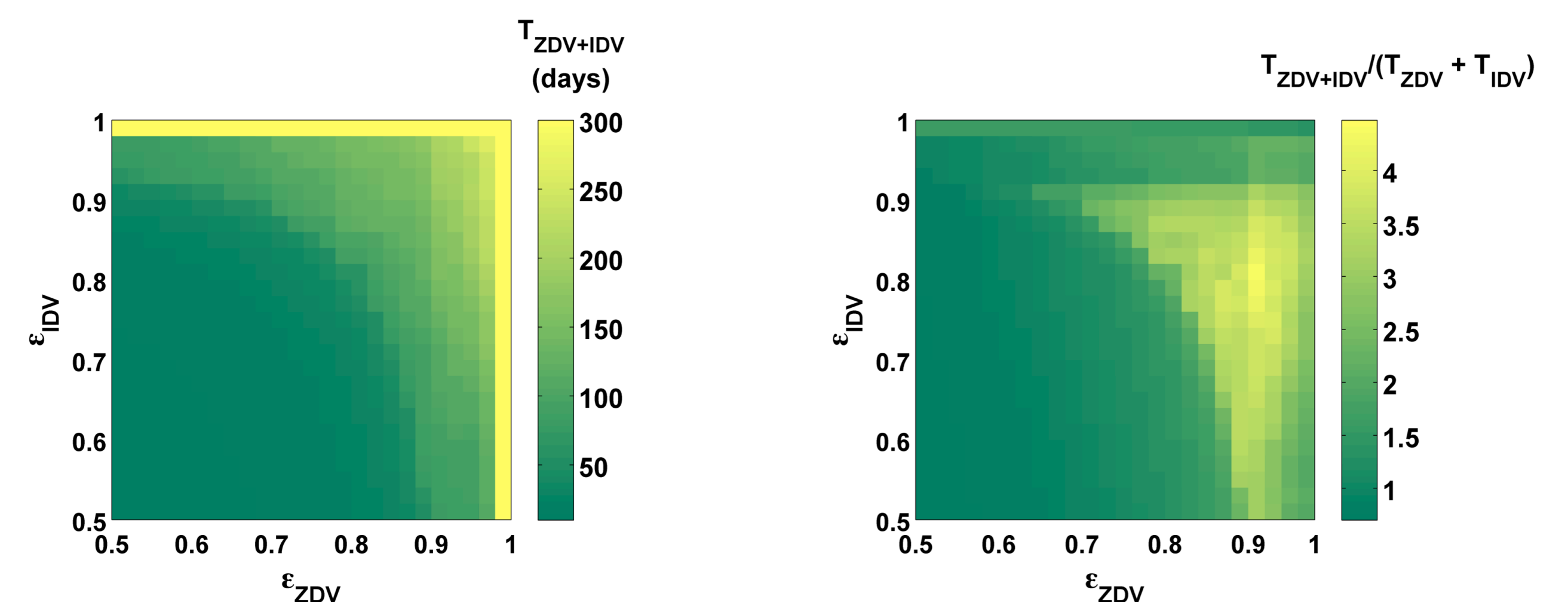


Figure 5

We computed the time to virological rebound and inferred that the time to failure with the combination was not a simple linear function of the time to failure with the individual drugs (Figure 5). In general predictors of treatment outcome under multiple drug therapy (for example, the genetic barriers to resistance, see [7]) are often assumed to be simple functions of the corresponding outcomes with monotherapy. Our results here serve as evidence for the limitations of such assumptions and reiterate the value of analysing multi-drug treatment regimens *in silico*.

Regularization:

Ridge regression enhanced the robustness of parameter estimation in such models (Figure 6). The existence of a critical ridge parameter ($\lambda = 0.045$) that stabilized fitness costs of all ZDV mutant genotypes was established. Further studies are needed to better understand the applications of such an approach in enhancing the stability of parameter estimation.

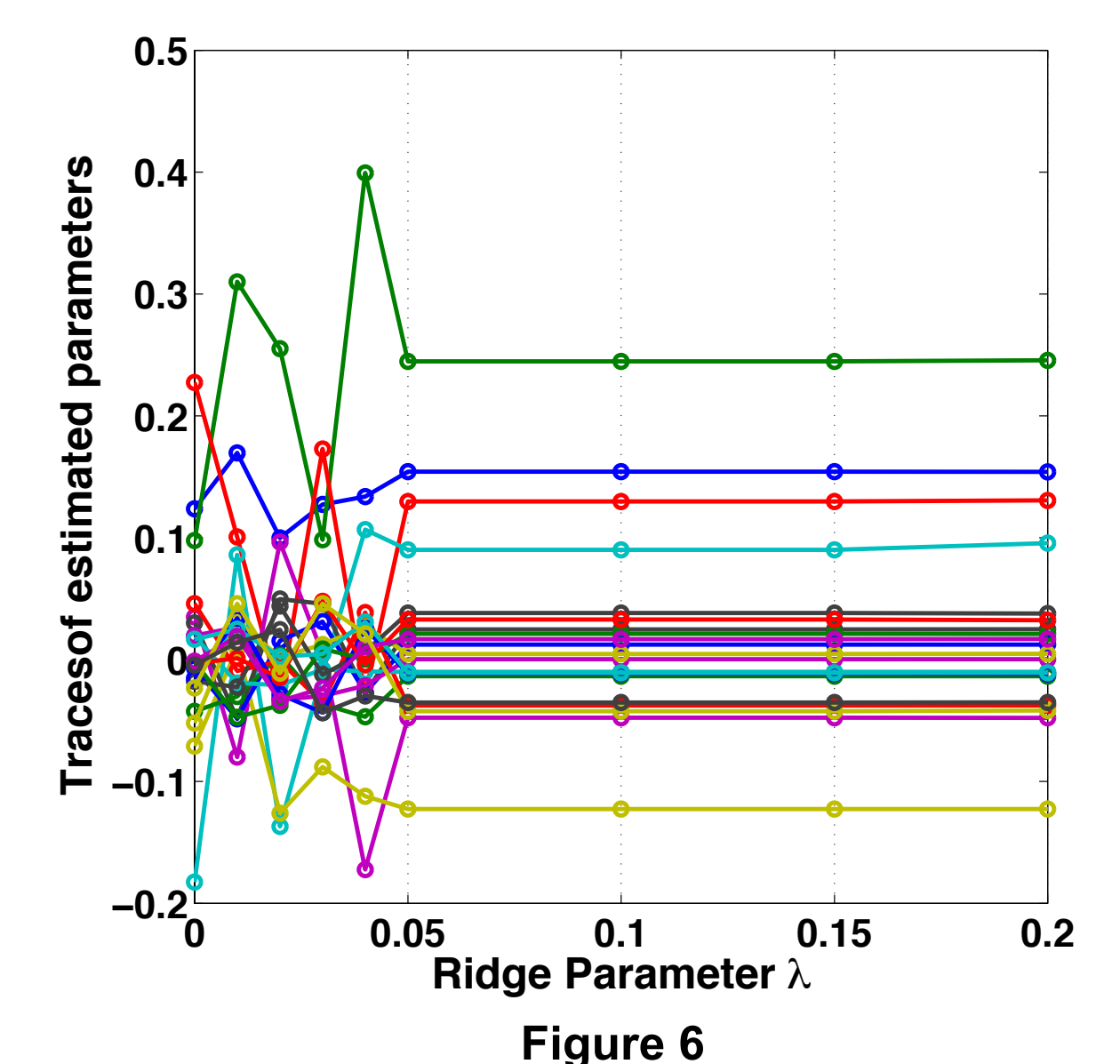


Figure 6

Conclusions

Our model with drug-specific mutation schemes utilized sparse clinical data to predict viral dynamics under combination regimens. This is a step towards studying potential salvage regimens upon treatment failure. Our approach also dissected the influence of individual drug efficacies on treatment outcome. Finally, we demonstrated the utility of regularization in stabilizing parameter estimation in such nonlinear models, that enables further use of our model.

References

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