

A Simple and Readily Integratable Approach to Toxicity Prediction

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A simple, highly extensible computational strategy to assess compound toxicity has been developed with the premise that a compound's toxicity can be gauged from the toxicities of structurally similar compounds. Using a reference set of 13645 compounds with reported acute toxicity endpoint dose data (oral, rat-LD₅₀ data normalized in mg/kg), a generic utility which assigns a compound the average toxicity of structurally similar compounds is shown to correlate well with reported values. In a leave-one-out simulation using the requirement that at least one structurally similar member in a "voting consortium" is present within a reference set, the strategy demonstrates a predictive correlation (q^2) of 0.82 with 57.3% of the compounds being predicted. Similar leave-one-out simulations on a set of 1781 drugs demonstrate a q^2 of 0.74 with 51.8% of the compounds being predicted. Simulations to optimize similarity cutoff definitions, consortium member size, and reference set size illustrate that a significant improvement in the quality and quantity of predictions can be obtained by increasing the reference set size. Similar application of the strategy to subchronic and chronic toxicity data should be possible given reasonably sized reference sets.

INTRODUCTION

Adverse drug reactions (ADRs) are the fifth leading cause of death.^{1–3} This alarmingly high figure is at the bane of a pharmaceutical industry that is already spending over \$800 million dollars over 10–15 years to develop a single new drug.⁴ And despite a tripling of R&D expenditures over the last 10 years, failure in the R&D process remains rampant and new chemical entity (NCE) development has stagnated.⁵

Numerous studies consistently cite the top three reasons for failure and slowdown in the development of NCEs as poor biopharmaceutical properties, lack of efficacy, and toxicity.^{6–8} Given a weaker economy and an aging population,^{9,10} drug developers cannot simply continue to escalate prescription drug prices.¹¹ To remain viable in the coming years, pharmaceutical companies must continue to contain R&D costs and make paramount the identification of compound failures sooner in the drug discovery process.^{12,13}

Unfortunately, all chemical substances can produce adverse health effects at some level of exposure. In acute toxicity, poisoning occurs after a single or short-term exposure causing severe biological harm or death. In chronic toxicity, poisonous effects (e.g. heart/liver damage, reproductive disorders, cancer, etc.) are seen after long term or repeated low level exposures. And while toxicological properties of a drug must be evaluated and documented in animals according to FDA regulations (Good Laboratory Practices) before study in humans, in which the safety of a drug is determined by studying the acute, subchronic, and chronic toxicity in several animal species,¹⁴ there still remains significant opportunity to proactively gauge the likelihood of toxic outcome earlier in the drug discovery process.

Several computational strategies exist for assessing potential toxicity,^{15–17} many of which are commercially avail-

able: DEREK,^{18–20} MCASE/CASETOX/TOX,^{21–25} TOPKAT,^{26,27} TOXAlert/HazardExpert,²⁸ TOXSYS,²⁹ CSGenoTox,³⁰ OncoLogic,³¹ etc. These programs generally utilize methodologies that leverage QSARs (e.g. TOPKAT), rule-based strategies (e.g. DEREK, HazardExpert, and OncoLogic), inductive logic (e.g. CASETOX), and combinations of each (e.g. MCASE). In general, each of the above programs requires either a new release of software or a computational expert to expand the scope of predicted behavior, thus making the addition of new reference-sets or rules based on newly acquired experimental data inconvenient or highly cumbersome. Finally, several of these strategies suffer from high-cost, difficult batch-mode integration (e.g. stodgy and/or legacy operating system implementation), closed or limited-proprietary knowledgebase and reference sets, and/or limited-predictive performance. Arguably, these limitations offer some explanation why computational toxicity assessment has not become as mainstream in early preclinical discovery as other computational methods³² which now appear embedded in "organizational awareness and self-discipline"⁶ (e.g. "rule of 5"³³). Given even a coarsely predictive, *readily accessible* toxicity assessment strategy, it is expected that organizations might realize a significant savings in time and resource provided they routinely prioritize-out compounds of probable toxic liability during early stage synthesis planning and compound acquisition activities.

MATERIALS AND METHODS

A starter reference set ("RefSet") of 13645 examples of oral, rat LD₅₀ data was assimilated from the Registry of Toxic Effects of Chemical Substances (RTECS) database.³⁴ The log of LD₅₀ in mg/kg (pLD50) for RefSet ranges from -3.85 to 5.27 with a mean of 2.92 and standard deviation of 0.85 (Supporting Information Figure S1). A subset of 1781 examples in the reference set ("DrugSet") was identified as

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Table 1. Reference Set (RefSet) and Drug Compound Subset (DrugSet) Physiochemical Properties^a

property	RefSet	DrugSet
N	13645	1781
MWT	304.1 (183.8)	367.4 (95.5)
CLOGP	2.1 (2.5)	2.9 (2.7)
QPlogS	-2.9 (2.4)	-3.9 (2.1)
TPSA	65.23 (70.4)	72.2 (48.3)
RotBonds	5.3 (5.5)	5.9 (4.2)

^a Average and (standard deviation) for N-number of compounds, MWT-molecular weight, CLOGP-predicted log of the octanol/water partition coefficient,³⁶ QPlogS-predicted aqueous solubility,³⁷ TPSA-calculated polar surface area,³⁸ RotBonds-number of rotatable bonds.

compounds that have been studied as medicinal agents in humans.³⁵ Table 1 highlights the average and standard deviations of some descriptive physiochemical properties for each set.

Each molecule was fingerprinted using the Daylight fingerprint toolkit³⁹ using a fingerprint size of 2048, which has proven useful in other applications.⁴⁰ While others have studied alternative molecular descriptors to help assess chemical similarity,⁴¹ Daylight fingerprints can be calculated very rapidly and often outperform many descriptors⁴² in assessing chemical similarity. An emphasis on the speed of calculation is particularly important, as a rapid, batch-based implementation is a necessary consideration. Daylight fingerprints encode all substructures in a molecule that contain from zero to seven bonds⁴³ in a manner that both describes and masks the originating structure. While Daylight fingerprint-based similarity calculation mostly leverages topological feature, inherent atomic feature and composite atom-through-bond feature described in these fingerprints can also help characterize geometric and electrostatic feature. It is expected that other “accepted” strategies that numerically characterize chemical structure en route to computing molecular similarity might perform comparably well or perhaps even better.

ASSESSMENT BY REFERENCE SIMILARITY

We have taken the premise that a compound’s toxicity (e.g. pLD50) can be gauged based on the toxicities of other structurally similar compounds. We have developed a generic utility “RefSim” (freely available at http://www.sertanty.com/ddd/refsim_request.html) that will attribute a property to a query compound based on the nonweighted average of that property across a reference set of compounds within a user-definable similarity cutoff. Because RefSim simply utilizes fingerprinted structures and associated numerical properties in a reference set to compute a predicted property, it can operate on compounds without knowing precise chemical structure or structural class. Furthermore, its generic nature affords the application to the study of other toxicity assessments (e.g. other subchronic/chronic endpoints). RefSim accepts a standard ASCII file format (Daylight-TDT) as input and will produce a file with the same format enriched with prediction values. Perhaps unlike other in silico methods to assess toxicity, RefSim has been designed for batch-mode implementation and can be readily integrated into most informatics systems.

Fundamental to this strategy is the notion that “like-behaves-like” and that a reasonably robust method to assign compound similarity exists. Several similarity metrics have

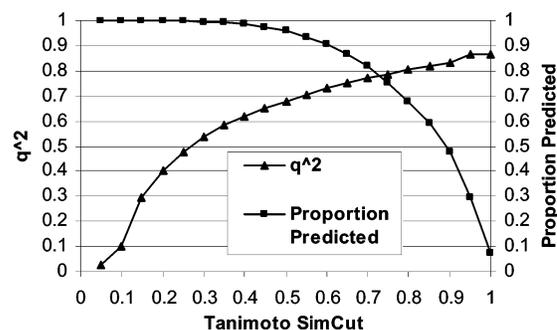


Figure 1. Prediction performance with increasing similarity cutoff. The triangles-curve (left Y-axis) shows an increase in predictive correlation (q^2) with an increasing Tanimoto similarity cutoff. The squares-curve (right Y-axis) shows a concomitant decrease in the proportion of predicted examples, given the requirement that a voting consortium must have at least one member. All leave-one-out simulations silenced the votes of consortium structures that exactly matched the query structure of interest.

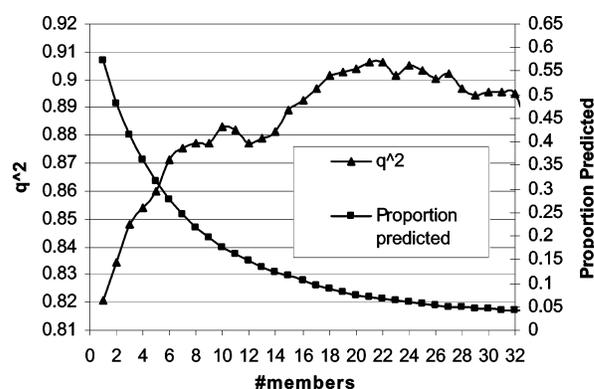


Figure 2. Prediction performance with increasing consortium size (similarity cutoff 0.75). The triangles-curve (left Y-axis) shows a general increase in predictive correlation (q^2) with an increasing number of members in a voting consortium. The squares-curve (right Y-axis) shows a general decrease in the proportion of predicted examples given the minimum consortium size. All leave-one-out simulations silenced the votes of consortium structures that exactly matched the query structure of interest.

been described in the literature.⁴⁴ RefSim utilizes the Tanimoto similarity metric but can readily accommodate other metrics (e.g. Euclidean, Tversky, etc.). A property prediction will be reported only if there are a minimum number of reference-set compounds within the defined similarity cutoff – i.e., a minimal “voting consortium” exists. No gain was achieved by weighting properties as a function of similarity measure, so all votes are considered equal in the calculation of the property average. Statistical assessments to compute leave-one-out cross-validated R^2 correlations (q^2) silenced the votes of consortium members with exact structural matches (i.e. exact string match between canonical SMILES) to the compound in question.

EXPERIMENTAL RESULTS

In applying RefSim to the assessment of pLD50, the two factors most dramatically effecting prediction performance and number of predictions are the user defined similarity cutoff and consortium size, Figures 1 and 2, respectively. Higher similarity cutoffs result in higher predictive performance but at the expense of the number of predictions made. An optimal similarity cutoff of 0.75 appears reasonable to maximize both the predictive performance and the number

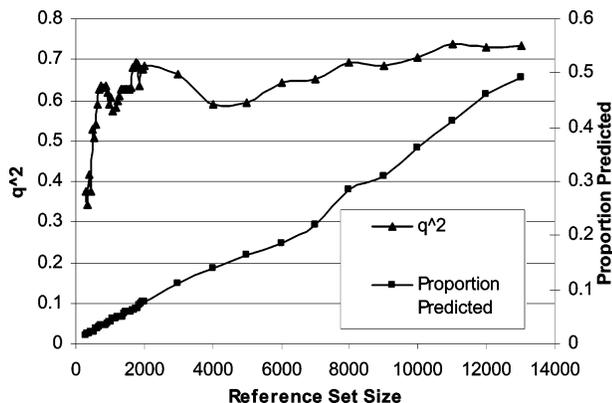


Figure 3. DrugSet prediction performance with increasing reference set size. The triangles-curve (left Y-axis) shows an early, rapid then more gradual improvement in predictive correlation (q^2) with increasing total RefSet size. The squares-curve (right Y-axis) shows a rapid increase in the proportion of predicted examples with increasing RefSet size. All simulations were leave-one-out with a similarity cutoff of 0.75 and a minimum voting consortium size of one.

of predictions made. Increasing the number of voting members generally results in an improvement of predictive performance, though having more than 20 members does not

appear to add significant predictive value. In general, there is a dramatic decrease in the proportion predicted with increasing minimal consortium size. Even with a consortium size of at least one member, less than 60% predictions are possible. This is all suggestive of a still “incomplete” reference set. Figure 3 further highlights the value of increasing the size of a reference set, suggesting that further increases to the reference set are likely to increase the scope of prediction. Unlike several of the above-mentioned commercially available toxicity prediction methods, RefSim can immediately leverage new additions to reference sets, without requiring a new version of software or having to go through a new rules-generation and/or QSAR redevelopment procedure.

Using a minimal consortium size of one and a similarity cutoff of 0.75, a leave-one-out simulation using the RefSet against itself demonstrated a predictive q^2 of 0.82 with 57.3% of the compounds being predicted (Supporting Information Figure S2). While this predictive performance is quite good, no predictions were made for nearly half of the compounds (i.e. 42.7%). This large not predicted proportion is a result of a significant number of “singletons” or reference set examples that share little similarity with other

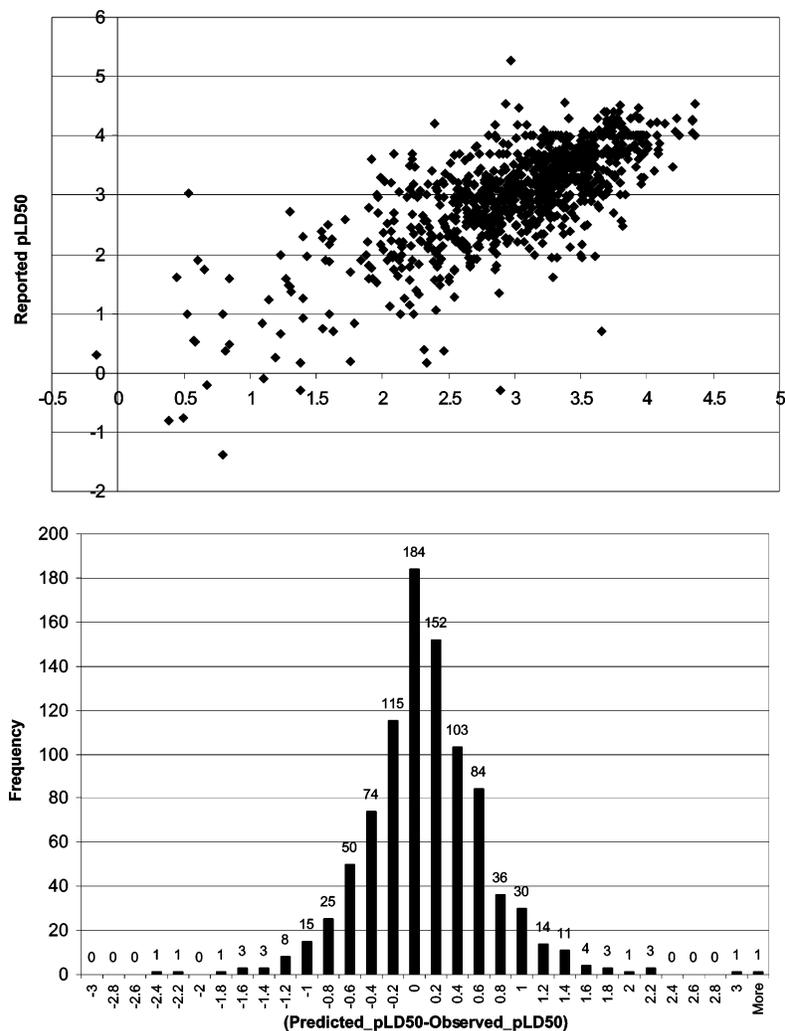
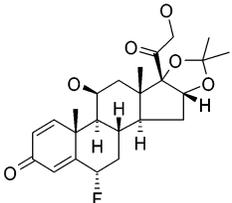
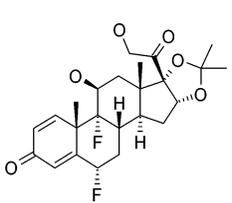
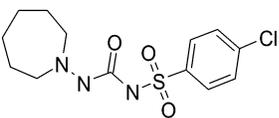
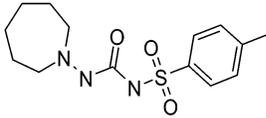
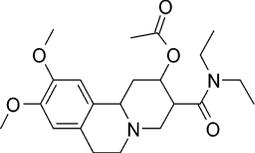
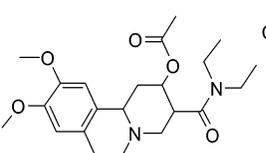
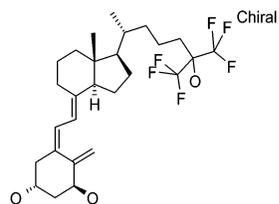
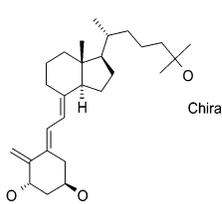
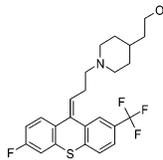
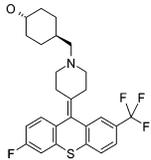
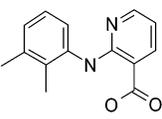
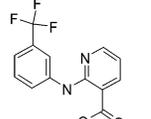
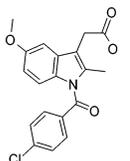
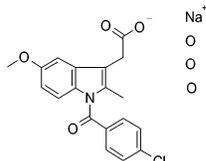
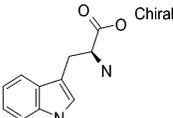
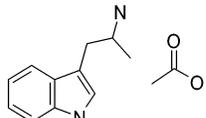


Figure 4. (A) DrugSet leave-one-out prediction performance simulation. Each of the 1781 DrugSet examples was considered in a leave-one-out simulation using the entire set of 13645 RefSet reference examples, a similarity cutoff of 0.75 and a minimum voting consortium of one. Predictive correlation (q^2) was 0.74 with 923 (51.8%) of the examples meeting the minimum consortium size criteria. (B) DrugSet prediction error distribution. For the 923 prediction examples in A, the absolute prediction error distribution indicates a fairly tight bounds with most errors (94%) falling within ± 1 pLD50 examples.

Table 2. DrugSet Prediction Outliers^a

DrugSet Molecule Name	DrugSet (DSM)	Molecule	DSM Observed LD ₅₀	RefSet Most Similar Molecule (RSM)	RSM Observed LD ₅₀	DSM Prediction Error: (Pred-Obs)	Num Ref Sim Mol	Tanimoto DSM& RSM
FLUNISOLIDE		Chiral	>500 µg/kg		>4 gm/kg	3.19	4	0.94
GLYPINAMIDE			>5 mg/kg		>5 gm/kg	2.96	2	0.87
BENZQUINAMIDE			1050 mg/kg		990 mg/kg	-2.48	2	0.99
FLOCACITRIOL		Chiral	41700 ng/kg		620 µg/kg	2.17	7	0.86
PIFLUTIXOLE			1500 µg/kg		>60 mg/kg	2.16	2	0.81
NIXYLIC ACID			2300 µg/kg		250 mg/kg	2.10	2	0.94
INDOMETHACIN			2420 µg/kg		21 mg/kg	1.93	24	0.86
TRYPTOPHAN		Chiral	>16 gm/kg		22 mg/kg	-1.81	4	0.99

^a The reported LD₅₀s for the query DrugSet molecules (DSMs) and for their respective maximally similar molecules in the reference set (RSMs) show significant differences despite high Tanimoto similarity between DSM and RSM. This helps explain the fairly large absolute, signed DSM prediction error: $pLD_{50}(\text{pred}) - pLD_{50}(\text{obs})$.

examples in the set. In a leave-one-out simulation, a singleton will have a consortium of one (itself), which would be silenced, and thus no prediction is made. The high proportion of singletons is again an indication that the reference set needs significant enrichment.

The average of the absolute value of prediction error (i.e. $\text{abs}(\text{Predicted}_pLD_{50} - \text{Observed}_pLD_{50})$) for the RefSet

leave-one-out-simulation is 0.34 with a standard deviation of 0.36 for the 7815 predictions made. Over 57% (4490/7815) of the predicted compounds are within ± 0.2 pLD₅₀ units of observed values, and over 95% (7463/7815) of the predictions are within ± 1 pLD₅₀ units. While it is clear the size and coverage of RefSet stands to be improved, it is a useful starting point.

A leave-one-out simulation with DrugSet, using RefSet as the reference set, demonstrated a predictive q^2 of 0.74 with 51.8% of the compounds being predicted (see Figure 4A). As before, almost half of the compounds (48.2%) did not have a voting consortium of at least one example, and thus no prediction could be made. Another observation that can be made from Figure 4A is the general tendency of DrugSet entries to have higher pLD50 values (i.e. lower acute toxicity). This is consistent with the tendency to progress only compounds with safer toxicity profiles and that compound failures typically go unpublished and/or remain hidden in company archives.

Figure 4B shows the distribution of prediction errors for the DrugSet leave-one-out simulation. Nearly 68% of the examples have a positive or zero prediction error (i.e. predicted-observed) value with 32% of the examples having a negative prediction error. Since less toxic compounds have higher observed pLD50s, predominance toward a positive prediction error might be worrisome, i.e., compounds predicted to be less toxic may actually be more so. However, almost 49% (451/923) of the predicted compounds are within ± 0.2 pLD50 units of observed values, and over 94% (868/923) of the predictions are within ± 1 pLD50 units. This level of predictive accuracy, while not perfect, can be of considerable value in an early discovery setting when a researcher is faced with a large number of synthetic possibilities and/or a large number of compound acquisition choices. If for no other reason than to flag compounds that might have potential toxic liability (given high similarity to one or more compounds in an ever growing knowledgebase of toxic precedence), this technique should offer some level of improvement over "blind faith" that a compound will be safe or that toxicity can be ameliorated later in the development cycle.

Table 2 highlights some of the top outliers in the DrugSet leave-one-out simulation. High structural similarity can be seen between the DrugSet molecule and the most similar member in the RefSet voting consortium. Of notable interest is the difference in reported LD₅₀s between salt forms of benzquinamide and indomethacin. Another notable difference in LD₅₀ is between flunisolide and its most similar RefSet member, where a simple H-to-Fluoro substitution results in a dramatic decrease in toxicity. Glypinamide is also a very dramatic outlier, with a single chloro-to-methyl substitution resulting in a very significant decrease in toxicity. It is not surprising these are predictive outliers, given the significant differences in LD₅₀ despite a high degree of observed structural similarity. While it is not clear if any predictive method would have fared well on these cases, it should be noted that none of the Tanimoto-similarity values between the DrugSet outlier and its maximally similar RefSet consortium member in Table 2 is 1.0 (albeit Benzquinamide is close) and all top outliers with the exception of indomethacin have a relatively small number of voting consortium members. Along with increasing RefSet's size, improvements in structure class coverage will likely decrease the number of predictive outliers.

SUMMARY AND CONCLUSIONS

Computational tools well-integrated into parallel preclinical discovery programs will allow early discovery researchers to increase their chances of arriving at more efficacious and

safer compounds, sooner and at lower cost.^{45,46} While a computationally predictive technology is not likely to replace later-stage clinical activities or early preclinical animal testing in the short-term, even a moderately predictive computational toxicity tool can play a significant role in helping to prune down early synthetic opportunities, compound acquisition choices, etc., especially when coupled with other tools to computationally evaluate a compound's preferred potency, ADME-biopharmaceutical properties, and oral availability.

Detailed information generated by a toxicity eScreen can be used by scientists to help prioritize compounds and to avoid work on compounds that are likely to fail in safety tests later in development. Reasonably accurate and robust toxicity predictions can be achieved with a reference similarity approach given a sizable, well-rounded reference set. Simulations have demonstrated that an increase in reference set size is likely to improve both the quality and quantity of toxicity predictions and decrease predictive outliers. Other simulations have demonstrated that small to moderate voting consortia per compound-class may suffice to build well-rounded reference sets, but current coverage even for known drug molecules is still fairly inadequate. Furthermore, because the described reference similarity technique utilizes structural fingerprints that do not directly reveal the specifics of any particular compound or structural class, competitive research organizations could share information into a collective pool without revealing a structural direction of their ongoing discovery efforts.

We would like to encourage the exchange of acute, subchronic, and chronic toxicity information throughout the pharmaceutical industry. In addition to making the RefSim utility freely available, we will commit to establishing a framework for organizations to submit and access encoded structure-fingerprint/toxicity-property information. Provided a critical mass of industrial participation, we hope to facilitate a cooperative assimilation of toxicity data with the expectation that all participants will benefit from improved toxicity models.

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Supporting Information Available: Distribution of the log₁₀ of LD₅₀ in mg/kg (pLD50) for the RefSet reference set; "RefSet" leave-one-out prediction performance simulation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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