

# Notes on RMSD inference

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✚ Note: the probability-theoretic derivations and explanations below are very concise and likely not fully comprehensible. I'll add some sections with clearer explanations and fuller derivations later on.

## 1 Overview

We consider a quantity, the Root-Mean-Squared Distance, denoted by  $y$ , and a set of quantities called “features”, denoted by  $x$ . A value of RMSD  $y$  and values for the features  $x$  can be associated with each target-ligand pair, which I'll call a “datapoint”.

Our problem is to infer  $y_0$  given:

- $x_0$  for a new datapoint,
- known pairs  $(\bar{y}, \bar{x}) := ((y_1, x_1), (y_2, x_1), \dots, (y_N, x_N))$  for other  $N$  datapoints,
- additional facts and hypotheses  $H$ .

Additional hypotheses are unavoidable since we are making an extrapolation.

Our uncertainty about  $y_0$  is expressed by the probability (density)

$$p(y_0 \mid x_0, \bar{y}, \bar{x}, H), \quad (1)$$

which we want to quantify.

The first question we must ask in approaching this problem is: how much does our uncertainty about  $y_0$  depend on the relative frequencies for previous datapoints  $(\bar{y}, \bar{x})$ ? For example, if  $y_0$  is hand-picked by someone, then knowledge of the frequencies for  $(\bar{y}, \bar{x})$  is irrelevant. But even in such a case it might be that the reversed probability

$p(x_0 | y_0, \bar{y}, \bar{x}, H)$  does depend on the frequencies of previous datapoints, and it can be used to calculate (1) as


$$p(y_0 | x_0, \bar{y}, \bar{x}, H) = \frac{p(x_0 | y_0, \bar{y}, \bar{x}, H) p(y_0 | H)}{\sum_{y_0} p(x_0 | y_0, \bar{y}, \bar{x}, H) p(y_0 | H)}. \quad (2)$$

The important difference between eqs (1) and (2) is that in the latter we must also quantify  $p(y_0 | H)$  using extra-data facts or hypotheses.

In technical terms we are asking whether  $y_0$  is *exchangeable* given  $x_0$ , or vice versa. Using Fisherian (1956 §§ II.4, IV.1) parlance we are asking whether  $y_0$  should be considered as belonging to a *subpopulation* determined by  $x_0$  or vice versa. (Or neither, in which case our study would simply end here, so we won't consider this third possibility.) Another way of seeing our question is whether “causal connections” (which can originate from a common cause) are more robust in the direction  $x_0 \rightsquigarrow y_0$  or  $y_0 \rightsquigarrow x_0$  (cf. Pearl 1988 §§ 2.1.2, 2.2.5).

This question is discussed in a brilliant paper by Lindley & Novick (1981), who show with examples its fundamental importance for making correct inferences. Exchangeability is the basic fact or assumption upon which machine-learning algorithms and the calculations presented here are based. A short intuitive summary of this notion is given in the next section.

We study both possibilities mentioned above. At the end we'll compare the results and discuss which assumption makes more sense in various applications.

The final goal is to compare the results of the present principled approach with those of machine-learning algorithms in a case where both can be used. More about this in  §\*\*\*.

## 2 Exchangeability, approximations, machine learning

Exchangeability is the fact or assumption that the ordering of known and yet unknown datapoints is irrelevant for new inferences. Good reviews are given by Dawid (2013) and Bernardo & Smith (1994 § 4.2).

A probability distribution  $p(z_0, z_1, z_2, \dots | H)$  is called *infinitely exchangeable* if it's invariant under permutations of the values  $z_0, z_1, \dots$ , no matter what and how many they are. In other words, the ordering of the observations doesn't matter. Usually one says, somewhat improperly,

that “ $z_0, z_1, \dots$  are exchangeable” for short. In our case each  $z$  is actually a pair of values  $(y, x)$ , where  $x$  itself is multidimensional.

Exchangeability has the following important consequence: if we knew the infinite-limit long-run relative frequencies  $F := (F_{y,x})$  of the values of past and future datapoints, then the probability of observing a sequence of new values would be equal to the long-run relative frequency of those values, for symmetry reasons. For example:

$$p(y_1, x_1, y_2, x_2 \mid F, H) = F_{y_1, x_1} F_{y_2, x_2} . \quad (3)$$

Another consequence is that conditional probabilities are also equal to the long-run *conditional* frequencies  $F_{y|x} := (F_{y|x}) = (F_{y,x} / \sum_{y'} F_{y',x})$ . For example:

$$p(y_1, y_2 \mid x_1, x_2, F, H) = F_{y_1|x_1} F_{y_2|x_2} . \quad (4)$$

If the long-run frequencies  $F$  are unknown, they can be marginalized, i.e. integrated out, provided that we have a probability distribution  $p(F \mid H)$  for them. For example:

$$p(y_1, x_1, y_2, x_2 \mid H) = \int F_{y_1, x_1} F_{y_2, x_2} p(F \mid H) dF , \quad (5)$$

from which we can also obtain conditional probabilities.

There are several other types of exchangeability. For example, we may have *conditional* or *partial* exchangeability of  $y$  given  $x$  if eq. (4) holds, but not eq. (3). If we have a probability distribution  $p(F_{y|x} \mid H)$  for the conditional frequencies, we obtain by marginalization

$$p(y_1, y_2 \mid x_1, x_2, H) = \int F_{y_1|x_1} F_{y_2|x_2} p(F_{y|x} \mid H) dF_{y|x} . \quad (6)$$

Lindley & Novick (1981) discuss the importance of conditional exchangeability for various inference problems, and the errors that arise if the wrong type of exchangeability is assumed.


From the generalization of the equations above we obtain other probabilities for various cases of regression, such as eqs (1) or (2), by simply using the three rules of the probability calculus. For example, if

$y_0$  is assumed to be exchangeable given  $x_0$ , but the latter is not assumed to be exchangeable with the other  $\bar{x}$  because hand-picked, we find

$$p(y_0 | x_0, \bar{y}, \bar{x}, H) = \frac{\int F_{y_0|x_0} F_{y_1,x_1} \cdots F_{y_N,x_N} p(F | H) dF}{\int F_{y_1,x_1} \cdots F_{y_N,x_N} p(F | H) dF}. \quad (7)$$

The distribution  $p(F | H)$ , usually called the “prior”, embodies the assumptions that we make for the extrapolation. It therefore cannot be determined by the known datapoints. Given enough known datapoints  $(\bar{y}, \bar{x})$ , the probability distribution for  $y_0$  given  $x_0$  eventually does become equal to their limit conditional frequency. This sets the ultimate uncertainty with which the prediction can be made, and cannot be surpassed by any algorithm. So this approach eventually does yield an optimal inference. The quickness with which the limit conditional frequency is reached, however, depends heavily on the choice of prior. The prior should therefore be chosen in a well-reasoned manner. In practice the choice is limited by computational constraints.

All machine-learning algorithms calculate equations such as the one above or approximations to it, for some choice of the prior  $p(F | H)$  (MacKay 1992a; Bishop 2006).

The formulae above can be numerically implemented exactly or with a good approximation only if the features  $x$  have low dimensions and the number  $N$  of known data is small  [add refs](#). Many machine-learning algorithms manage to deal with larger dimensionality and datapoints by parametrizing the  $F$ -space in a clever way (for example, deep nets parametrize the  $F$  as nested compositions of some simple functions) and finding an argument that maximizes the integrands above (MacKay 1992a,b), for example a value of  $y_0$  that locally maximizes the integrand in the numerator of eq. (7). This means, though, that they cannot quantify the uncertainty of the inference.

### 3 Direct case: methodology

For the direct case (1) we consider the RMSD  $y$  as a continuous variable, mapped to a log-scale to avoid dealing with finite ranges.

In the direct case the assumption is that  $y_0$  is exchangeable given  $x_0$ , but  $x_0$  is not exchangeable given the known datapoints  $\bar{x}$ . This is a sensible assumption – a fact indeed – if we are *choosing* the specific value

of  $x_0$ , as we do in some testing situations for example. The values  $(\bar{y}, \bar{x})$  are considered exchangeable.


The probability  $p(y_0 | x_0, \bar{y}, \bar{x}, H)$  is then given by eq. (7), which can be rewritten this way:

$$p(y_0 | x_0, \bar{y}, \bar{x}, H) = \int F_{y_0|x_0} p(F | \bar{y}, \bar{x}, H) dF$$

$$\text{with } p(F | \bar{y}, \bar{x}, H) = \frac{F_{y_1, x_1} \cdots F_{y_N, x_N} p(F | H)}{\int F_{y_1, x_1} \cdots F_{y_N, x_N} p(F | H) dF}, \quad (8)$$

which is the main formula of the direct case.

The integrals are over the set of long-run joint frequency distributions, which is an infinite-dimensional manifold. A currently popular way to parametrize it and at the same time choose a prior  $p(F | H)$  is by means of so-called Dirichlet-process mixtures. In short, a generic  $F_{y,x}$  is represented as a countable weighted sum of a simpler distribution  $K$ , called the kernel, with different parameters:  $F_{y,x} = \sum_i w_i K(y, x | \theta_i)$ . The prior is therefore defined over the possible infinite tuples  $(w_i, \theta_i)$ . A Dirichlet process is chosen as such prior. In the present case the kernel is the product of a multivariate normal distribution for  $y$  and for the continuous features in  $x$ , and a Dirichlet distribution for the discrete features in  $x$  (Liverani et al. 2015 § 3.3). An example of this approach is analysed and used by Müller et al. (1996). A discussion of why such a choice of prior may not be sensible is discussed by Petrone (2017) and Quintana et al. (2020 § 4).

The first integral in eq. (8) is numerically approximated by a sum of values of  $F_{y_0|x_0}$  sampled from the distribution  $p(F | \bar{y}, \bar{x}, H)$  via Markov-chain Monte Carlo methods. Details about the sampling algorithm are given in  §\*\*\*.

## 4 Reverse case: methodology

For the reverse case (2) we consider a binned RMSD divided into three categories:  $y \in \{\text{'good'}, \text{'inconclusive'}, \text{'bad'}\}$ .

In the reverse case the assumption is that  $x_0$  is exchangeable given  $y_0$ , but  $y_0$  is not exchangeable given the known datapoints  $\bar{y}$ . This is again a sensible assumption if we are choosing the specific value of  $x_0$ , as we do in testing situations, because then  $y_0$  cannot be considered to come from


some unsystematic process, if it has some causal connections with  $x_0$ . The values  $(\bar{y}, \bar{x})$  are considered exchangeable.

The probability  $p(x_0 | y_0, \bar{y}, \bar{x}, H)$  is obtained analogously to eq. (6), reversing the roles of  $y$  and  $x$ . We make the additional assumption that the prior  $p(F_{x|y} | H)$  factorizes for the frequencies conditional on the three  $y$  categories:

$$p(F_{x|y} | H) = p(F_{x|good} | H) \cdot p(F_{x|inconcl.} | H) \cdot p(F_{x|bad} | H). \quad (9)$$

The result is three distinct conditional probabilities:

$$\begin{aligned} p(x_0 | y, \bar{y}, \bar{x}, H) &= \int F_{x_0|y} p(F_{x|y} | \bar{x}, H) dF_{x|y} \\ p(F_{x|y} | \bar{x}, H) &= \frac{F_{x_{1'}|y} \cdots F_{x_{N'}|y} p(F_{x|y} | H)}{\int F_{x_{1'}|y} \cdots F_{x_{N'}|y} p(F_{x|y} | H) dF_{x|y}} \quad (10) \\ &\text{for each } y \in \{\text{'good'}, \text{'inconclusive'}, \text{'bad'}\}, \end{aligned}$$

where the conditionals contain only  $\bar{x}$  values associated with that specific  $y$  value ( I'll find clearer notation and explanations).

The fact that we have three distinct conditional probability distributions allows us to split the computation into three. They can be done in parallel and each has one less dimension and is being conditioned on fewer data, so the computation is somewhat faster.

The computation of each probability is analogous to that explained in § 3, based on a Dirichlet-process mixture with product kernels of multivariate normal and Dirichlet distributions.

## 5 Evaluation metrics and calibration

### Appendices

 These are just working notes

#### A Notes on selection of prior

The “sasa” quantities  $x$  have a range in  $[0, +\infty[$ . We consider them as scale quantities (even if the value 0 is included) and transform them to a

log-scale. Their prior distribution is chosen as almost uniform on this scale:  $p(\ln(x) | H) \propto d \ln(x)$ , approximated by a normal with large standard deviation.

The “tanimoto” quantities  $x$  have a range in  $[0, 1]$ . We transform them to  $\mathbf{R}$  using the cumulative normal distribution:

$$x \mapsto \phi(x) := \frac{1}{2} \operatorname{erf}\left(\frac{x}{\sqrt{2}}\right) \equiv \frac{1}{\sqrt{2\pi}} \int_{-\infty}^x e^{-t^2/2} dt, \quad (11)$$

which we call an ‘erf-scale’. The prior is chosen as uniform in  $dx$ , and therefore has a standard normal density in the erf-scale.

Choosing a normal-inverse-Wishart distribution with parameters  $\mu^*, \Delta^*, \kappa^*, \nu^*$  as the mean for the Dirichlet process leads to a t-distribution as the predictive distribution for a quantity  $x \in \mathbf{R}^d$ , with  $\nu^* - n + 1$  degrees of freedom, mean  $\mu^*$ , covariance  $\frac{\kappa^* + 1}{\kappa^* (\nu^* - d - 1)} \Delta^*$ .

This means that we want  $\nu^* - n + 1$  large, say  $\sim 10$ , in order to approximate a normal,  $\mu^*$  equal to the zero vector, and  $\frac{\kappa^* + 1}{\kappa^* (\nu^* - d - 1)} \Delta^*$  diagonal and equal to 1 in the direction of the “tanimoto” quantities, and equal to some larger value in the direction of the “sasa” quantities. This leaves the parameter  $\kappa^*$  undefined.

## Bibliography

(“de  $X$ ” is listed under  $D$ , “van  $X$ ” under  $V$ , and so on, regardless of national conventions.)

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