**Predictive models of deep molecular response to imatinib treatment in chronic myeloid leukemia patients**

**Running title:** Predictive models of deep molecular response in CML patients

**Authors:** Zahra Zad,1 Simone Bonecker,2 Taiyao Wang,1 Jordana Ramires,2 Ilana Zalcberg, 2 Luciana Mayumi Gutiyama,2 Julia L. Fleck,3 and Ioannis Ch. Paschalidis, Ph.D.1\*

1Department of Electrical and Computer Engineering, Department of Biomedical Engineering, Division of Systems Engineering, and Faculty of Computing & Data Sciences,

Boston University, Boston, MA

2 Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil.

3Mines Saint-Etienne, Univ Clermont Auvergne, CNRS, UMR 6158 LIMOS, Centre CIS, F – 42023 Saint-Etienne, France.

**\*Corresponding author:**

Ioannis Ch. Paschalidis, Department of Electrical and Computer Engineering, Division of Systems Engineering, Department of Biomedical Engineering, and Faculty of Computing & Data Sciences, Boston University, 8 Saint Mary’s St., Boston 02215, MA, USA.

Email: [yannisp@bu.edu](mailto:yannisp@bu.edu)

Tel: 617-353-0434

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To the editor:

Chronic Myeloid Leukemia (CML) is a myeloproliferative disease leading to a significant accumulation of circulating leukemic cells.1 These cells are characterized by the presence of the Philadelphia chromosome (Ph), resultant of translocation t(9;22).2 This translocation gives rise to the fusion gene BCR-ABL13-7

Estimates put CML to comprise about 15% of all leukemia cases. It is expected that about 1 person for every 526 in the U.S. will suffer from CML during their lifetime.8 In 2022, about 9,000 new CML cases are expected in the U.S. (at a rate of 2.7 per 100,000 inhabitants) and about 1200 deaths.8 In Brazil, where our data originated, the incidence rate has been estimated to be about 1.5 per 100,000 inhabitants.9

The actionable gene fusion led to the development of specific and effective tyrosine kinase inhibitors (TKI), used until today, after more than 20 years.10 TKI therapy has profoundly changed the CML landscape since leukemia is not the major cause of death among Ph+ patients.11 The new perspective that has emerged considers a patient's optimal long-term management which seeks to reach and maintain a stable Deep Molecular Response (DMR) and discontinue medication when achieving Treatment-Free Remission (TFR).12

Monitoring the response to TKI treatment is carried out by quantitative polymerase chain reaction (qPCR) at determined timepoints, as recommended by the European Leukemia Net (ELN). Changing TKI must be considered if molecular milestones are not reached or the patient presents some clinical intolerance to treatment.13

Molecular response (MR) is reported according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts, as BCR-ABL1 % on a log scale. Major Molecular Response (MMR) has been defined as achieving MR3.0 or greater and DMR by the more stringent criteria of ≥MR4.0, which means BCR-ABL1<0.01%.14

Patients with a stable DMR are considered for discontinuing further treatment. TFR can be considered the new goal of CML management. The current most relevant issues for CML are to increase the number of patients eligible for TFR and to decrease the rate of patients who progress to the stage of blast crisis.15 With this motivation, in this study we sought to provide an earlier and better recognition of patients more likely to achieve DMR by developing predictive models that classify patients into those who achieve DMR and those who do not. Such models have the potential to identify a patient with a low likelihood of reaching DMR at ELN milestones, thus improving the management of refractory disease by increasing the therapeutic window for changing TKI treatment or by an earlier indication of hematopoietic stem cell transplantation before patients progress to blast crisis.

Since there is significant heterogeneity in CML outcomes, models for predicting resistance, risk of progression, or sustained molecular response after therapy, are limited. This study developed predictive models of achieving DMR for CML patients treated with imatinib. We used the patients’ clinical data and BCR-ABL1IS quantification in the early stages of treatment to predict whether they achieve DMR at later treatment stages. We also sought to inform drug discontinuation decisions by predicting the achievement of long-term DMR, namely, reaching DMR at 24 months from treatment initiation and maintaining this status until 60 months. The proposed models include linear and non-linear classification methods and were developed based on a dataset of 144 CML patients from the Brazilian National Cancer Institute (INCA).

We compared results from L2 and L1-penalized logistic regression (L2LR and L1LR, respectively), with the two SVM variants, the Random Forest (RF), the Gradient Boosted Trees (LightGBM), and the feed forward Multilayer Perceptron Neural Networks (MLP) (Table 1). Table 1 shows the mean and standard deviation of AUC and weighted-F1 score on the test set over the twenty repetitions using all variables selected by statistical feature selection and recursive feature elimination (parsimonious models).

The median of the patient’s recorded BCR-ABL1 ratios and white blood cell count at diagnosis (time 0) are among the most important predictive variables. In model\_6\_18, the achievement of MMR is an important predictor. The AUC of the best parsimonious models is 86.1% for model\_6\_18, 85.4% for model\_3\_18, 89.7% for model\_6\_12, and 86.2% for model\_long\_12. Figure 1 shows the evolution of the best AUC we can achieve with our models.

The best AUCs achieved by the three models are between 85% and 89%, using only two variables. This suggests moderate to strong predictive power for DMR shorter term (the first three models) but also longer-term (model\_long\_12), informing physicians on how to optimize treatment but also recommending discontinuing treatment upon achieving TFR.

The most important predictive variables are: the median of the patient’s recorded BCR-ABL1 ratios, the white blood cell count at the time of diagnosis, and the achievement of MMR in the three month interval starting at 3 months after IM treatment initiation and extending to 6 months (Table 2). The first two variables have negative coefficients, implying that larger values of these variables lead to a smaller probability of achieving DMR, which is in agreement with medical intuition and the literature. In particular, it is well known that higher values of the BCR-ABL1 ratio and white blood cell count at diagnosis indicates poor prognosis and thus, the achievement of DMR is less likely.8 The third variable, the achievement of MMR in the [3,6] month interval, has a positive coefficient and implies an increased likelihood of achieving DMR at 18 months. For example, in model\_6\_18 we have that 59% of patients with recorded BCR-ABL1 < 0.01 at 3 to 6 months after start of IM achieve DMR in 18 months.

Nevertheless, our results are in agreement with recent data which indicates that patients with an early molecular response have a higher probability of achieving DMR16, since those patients will have smaller BCR-ABL1 median and will achieve MMR before 6 months of treatment.

Stopping TKI treatment is a safe option which especially benefits patients with comorbidities and the young, providing a higher quality of life and reducing costs. At present, monthly BCR-ABL1 transcript level monitoring is recommended during the first 12 months after stopping TKI to detect early loss of MMR.17-19 To our knowledge, this is the first study to model DMR using data from a Brazilian cohort of CML patients. Results shown here reveal that the probability of reaching DMR can be predicted with high accuracy. The models can inform decisions to discontinue TKI for patients with no side effects.

Before publication, we will make available on-line modules implementing the models for anyone to use. De-identified data from the CML patients at the Brazilian National Cancer Institute (INCA) can be made available to individual researchers upon a reasonable request to the authors.

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**Tables**

*Table 1*. *Test set performance of the parsimonious models using LR, SVM, RF, MLP, and LightGBM.*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | model\_6\_18 | | | | model\_3\_18 | | | | model\_6\_12 | | | | model\_long\_12 | | | |
|  | AUC | | weighted\_F1\_score | | AUC | | weighted\_F1\_score | | AUC | | weighted\_F1\_score | | AUC | | weighted\_F1\_score | |
|  | mean | std | mean | std | mean | std | mean | std | mean | std | mean | std | mean | std | mean | std |
| L2LR | 84.7% | 8.3% | 81.2% | 5.8% | 84.3% | 7.6% | 81.8% | 5.4% | 78.5% | 11.9% | 81.4% | 5.1% | 83.4% | 10.3% | 82.9% | 3.6% |
| L1LR | 85.7% | 8.3% | 81.5% | 5.6% | 85.4% | 6.9% | 83.5% | 6.3% | 76.7% | 13.3% | 81.5% | 5.3% | 85.6% | 8.5% | 84.3% | 4.3% |
| L1SVM | 86.1% | 5.5% | 82.0% | 4.4% | 85.3% | 7.1% | 83.5% | 5.8% | 77.5% | 12.4% | 80.8% | 4.9% | 86.2% | 8.1% | 84.9% | 4.6% |
| L2SVM | 84.6% | 8.4% | 81.5% | 5.6% | 84.4% | 7.4% | 81.3% | 6.1% | 78.4% | 11.6% | 81.7% | 5.2% | 84.7% | 9.7% | 85.6% | 5.2% |
| RF | 83.3% | 7.9% | 81.0% | 6.6% | 83.7% | 11.2% | 80.0% | 6.9% | 89.3% | 5.7% | 90.2% | 4.4% | 78.4% | 14.6% | 81.1% | 4.3% |
| MLP | 83.3% | 11.9% | 83.1% | 7.2% | 84.9% | 8.0% | 81.9% | 5.2% | 81.1% | 11.6% | 83.2% | 4.9% | 77.8% | 12.0% | 79.9% | 3.9% |
| LightGBM | 81.8% | 6.8% | 78.6% | 5.6% | 83.6% | 11.1% | 78.2% | 6.0% | 83.4% | 10.3% | 86.1% | 4.6% | 80.8% | 10.2% | 83.7% | 6.0% |

*Table 2. We list the LR coefficients of each variable (Coef), the correlation of the variable with the outcome (Y-corr), the mean of the variable (Y1-mean) in the patients achieving DMR at the time corresponding to each model, and the mean of the variable (Y0-mean) in the remaining (non-DMR) patients.*

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Coef | Variable | All\_mean | All\_std | y1\_mean | y1\_std | y0\_mean | y0\_std | p-value | y\_corr |
| model\_6\_18 parsimonious model's features | | | | | | | | | |
| -3.10 | Median of Bcr-Abl ratios | 10.15 | 16.6 | 1.8 | 3.56 | 12.97 | 18.27 | 2.95E-07 | -0.29 |
| 0.31 | MMR\_3\_6 | 33% | 47% | 59% | 50% | 25% | 43% | 3.22E-02 | 0.32 |
| model\_3\_18 parsimonious model's features | | | | | | | | | |
| -2.05 | Median of Bcr-Abl ratios | 14.96 | 22.28 | 2.92 | 5.44 | 19.17 | 24.35 | 4.19E-07 | -0.32 |
| -0.75 | WBC count at diagnosis | 119631.36 | 95581.02 | 86850 | 70706.17 | 131104.83 | 100877.99 | 3.14E-02 | -0.20 |
| model\_6\_12 parsimonious model's features | | | | | | | | | |
| -0.14 | WBC count at diagnosis | 125161.63 | 102512.6 | 59113.08 | 33837.24 | 134597.14 | 105612.36 | 8.50E-03 | -0.24 |
| -0.07 | Median of Bcr-Abl ratios | 10.27 | 16.62 | 2.62 | 6.87 | 11.37 | 17.32 | 3.00E-06 | -0.18 |
| model\_long\_12 parsimonious model's features | | | | | | | | | |
| -4.72 | Median of Bcr-Abl ratios | 4.47 | 10.15 | 0.2 | 0.36 | 5.15 | 10.78 | 3.37E-04 | -0.17 |
| -1.55 | WBC count at diagnosis | 115829.05 | 93768.24 | 63507.69 | 43228.72 | 124123.9 | 97045.17 | 1.86E-02 | -0.22 |

Abbreviations: MMR\_3\_6 indicates achieving Major Molecular Response (MMR, defined as ≥MR3.0)

In the 3-month interval from 3 to 6 months after the start of IM.

**Figures**

Chart, bar chart

Description automatically generated

*Figure 1. Evolution of the best AUC we can achieve for predictions at 12, 18, and 60 months.*

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