MODELING THE PHARMACODYNAMICS OF DOPING DRUGS AND ANALYSIS OF FALSE NEGATIVE TESTS

Özge Şahin[a], Feyyaz Şentürk[b], Yaman Barlas[b], Hakan Yaşarcan[b]

[a] Department of Mathematics
Technical University of Munich
85748 Garching bei München, Munich, Germany
ozge.sahin@tum.de

[b] Industrial Engineering Department
Boğaziçi University
34342 Bebek Istanbul Turkey
+90 212 359 73 43
feyyaz.senturk@boun.edu.tr, ybarlas@boun.edu.tr, hakan.yasarcan@boun.edu.tr

Keywords: nandrolone dynamics, finasteride, false negative doping tests, biomedical modeling, pharmacodynamics modeling

In this study, a model for the dynamics of nandrolone, an anabolic steroid, in human body is constructed. Firstly, the model generates the dynamics of nandrolone only and its metabolites in the body. Secondly, we design different scenarios to see how nandrolone users can cheat in performance enhancing drug (PED) tests. PED tests for nandrolone check for the presence of 19-NA. Thus, to cheat the tests, PED users typically also use inhibitors of 19-NA such as Finasteride, a drug primarily used to cure male balding and prostate growth. Actually, Finasteride does not have a direct effect on 19-NA; its main effect in the body is the inhibition of enzymes that turn nandrolone into its metabolite 19-NA. Accordingly, we include structures for Finasteride and reductase enzymes in the model.
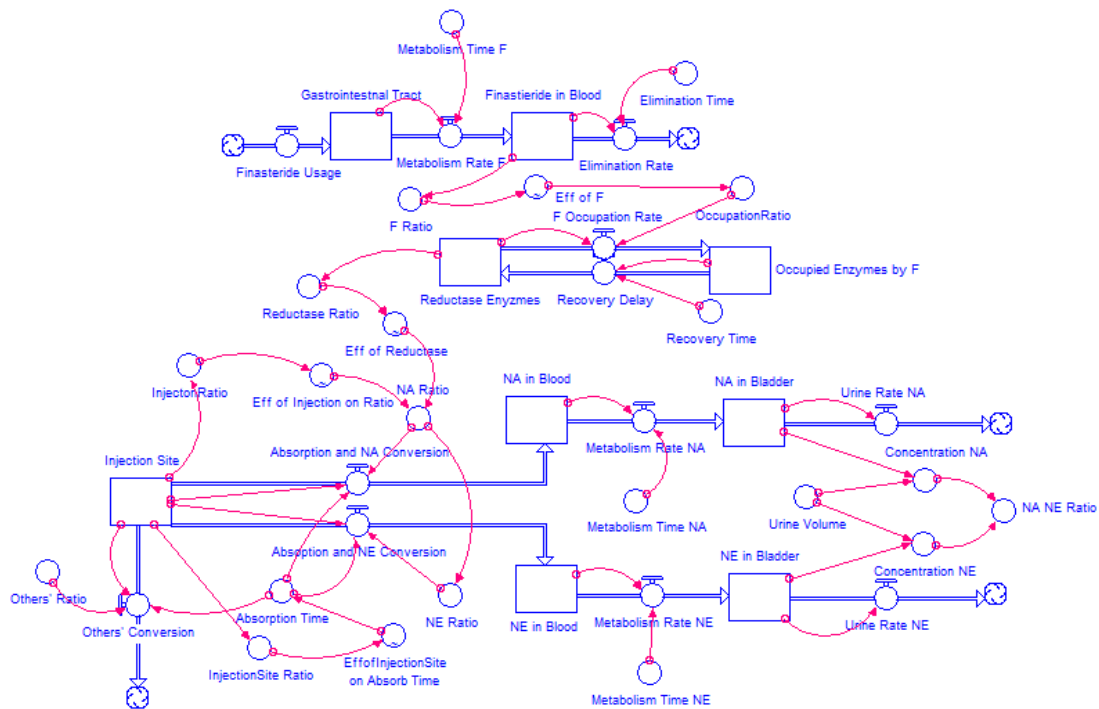

Figure 1: Simplified Model Structure

Injection Site, Finasteride in Blood, NA in Blood, NE in Blood and Reductase Enzymes are the key variables that we are interested in. Model validation is carried out by utilizing three runs and comparing the results to literature. The first run involved no intake of nandrolone and finasteride. Second run involved the injection of 150 mg of nandrolone decanoate. The results of the run and the comparison to real data can be seen in figure 2 and figure 3. Third run is done by intake of 5mg of

finasteride with the injection of 150 mg nandrolone decanoate. The model-generated dynamics are consistent with the reviewed literature.
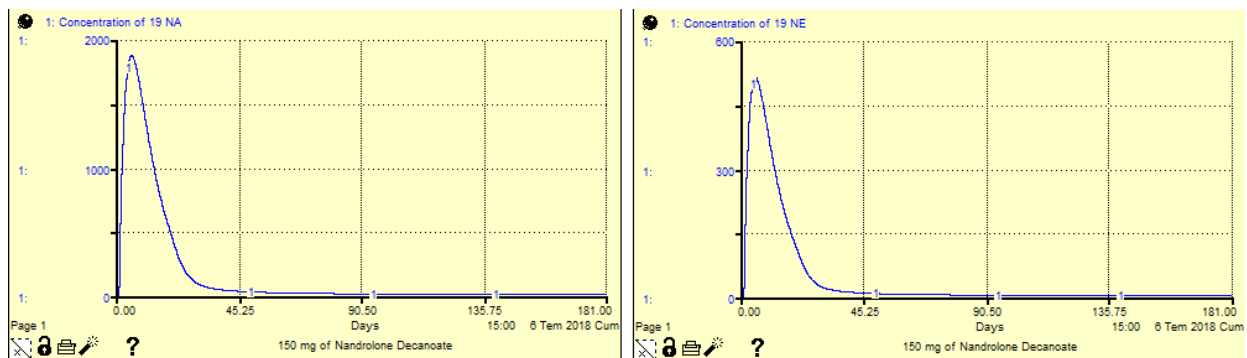

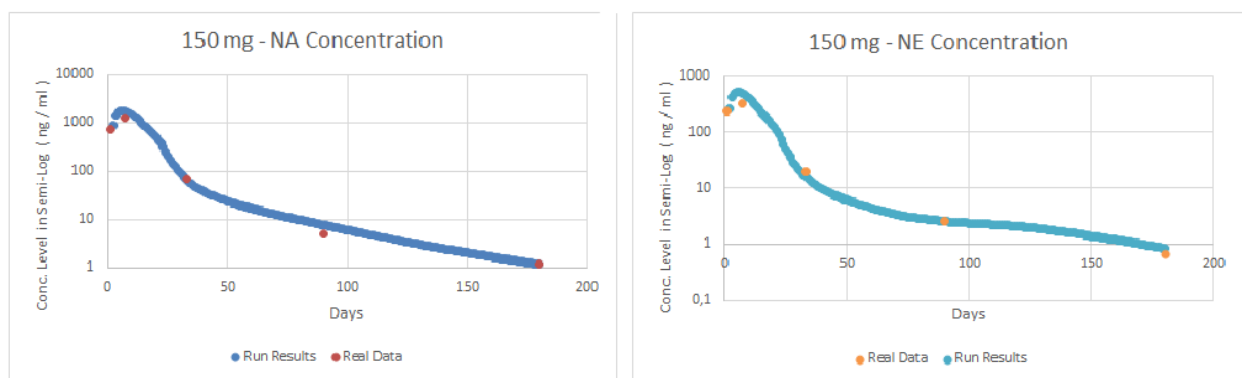Figure 2: Behavior Validity Run

Figure 3: Real Data for Comparison

We test different ways of cheating the PED tests using scenario analyses with Finasteride. An example scenario can be seen in figure 4.
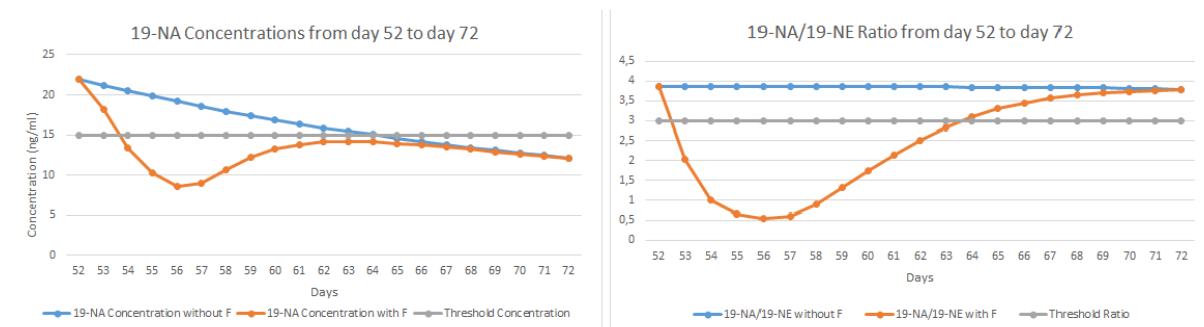

Figure 4: A False Negative Scenario Example

Our scenarios showed that besides decreasing 19-NA excretion, finasteride also decreased the 19-NA/19-NE (another metabolite of nandrolone) ratio, one of WADA's security measures. To get around this effect, WADA should take frequent samples during the competitions. If any sample has an increasing 19-NA/19-NE ratio, WADA should flag the sample and closely follow that athlete. Alternatively, a threshold for 19-NE can be considered. False positive cases can be implemented into the model in future work. Model can also be modified to account for other similar anabolic steroids.

REFERENCES

1. Martin David M., Baron David A., Gold Mark S. A Review of Performance-Enhancing Drugs in Professional Sports and Their Spread to Amateur Athletics, Adolescents, and Other At-Risk Populations. Journal of Addictive Diseases; Sep. 2008

2. Kickman Andrew T., Gower DB. Anabolic steroids in sports: Biochemical, clinical and analytical perspectives. Annals of Clinical Biochemistry; July 2003, 321

3. Hemmersbach Peter, Grobe Joachim. Nandrolone: A Multi-Faceted Doping Agent. Doping in Sports. Springer; 2009:128 – 148.

4. World Anti-Doping Agency (2017) Harmonization of Analysis and Reporting of 19-Norsteroids Related to Nandrolone Available at https://www.wada-ama.org/en/resources/science-medicine/td2017na

5. Cadwallader Amy B., de la Torre Xavier, Tieri Alessandra, Botre Francesco, The abuse of diuretics as performance-enhancing drugs and masking agents in sport doping: pharmacology, toxicology and analysis. British Journal of Pharmacology; Sep 2010.

6. Suzuiki Rie, Satoh Hiroki, Ohtani Hisakazu, Hori Satoko, Sawada Yausufmi, Saturable Binding of Finasteride to Steroid 5-alpha Reductase as Determinant of Nonlinear Pharmacokinetics. Drug Metab. Pharmacokinet.; 2010

7. Schanzer W., Geyer H.,Nolteernsting E., Finasteride-A Substance for Manipulation in Dope Control. Recent Advances in Doping Analysis(7); 1999

8. "Urine 24-Hour Volume." MedlinePlus Medical Encyclopedia, medlineplus.gov/ency/article/003425.htm.

9. Bagchus Wilma M., Smeets Jean M. W., Verheul Herman A. M., De Jager-Van Der Veen Suzanne M., Port Andreas, Geurts T. B. Paul. Pharmacokinetic Evaluation of Three Different Intramuscular Doses of Nandrolone Decanoate: Analysis of Serum and Urine Samples in Healthy Man. The Journal of Clinical Endocrinology; 2005:2624.

10. World Anti-Doping Agency (2015) Excretion of 19 Nor-Steroids from Consumption of Pork Meat and Offal: Combined GC/MS and GC/C/IRMS Analysis Available at https://www.wada-ama.org/en/resources/science-medicine/excretion-of-19-nor-steroids-from-consumption-of-pork-meat-and-offal

11. Geyer H., Gorius I., Dreyer N., Mareck U., Thevis M., Schanzer W. Investigation about the effects and the detection of finasteride. Recent advances in doping analysis (13); 2005

12. Finn Deborah A., Beadles-Bohling Amy S., Beckley Ethan H., Ford Matthew M., Gililland Katherine R., Gorin-Meyer Rebecca E., Wiren Kristine M. A New Look at the 5alpha-Reductase Inhibitor Finasteride.