

MODELING THE PHARMACODYNAMICS OF rHuEPO, A BLOOD DOPING DRUG

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For this study, we construct a model to analyse the dynamic effects of *recombinant human erythropoietin* (rHuEPO), a very popular and hard to detect blood doping drug. rHuEPO is the synthetic version of *erythropoietin* hormone which is responsible for the red blood cell production. Erythropoietin hormone is regulated in the body depending on the changes in blood oxygen levels due to various external factors such as a change in altitude and a change in the oxygen ratio in the surrounding environment (Figure 1). rHuEPO is mainly used as a therapeutic drug for anemia patients. However, athletes use rHuEPO to increase their red blood cell mass, thus, increasing their oxygen carrying capacity. This gives them unfair advantage in many sports such as running, cycling, swimming etc. For this reason, usage of rHuEPO or other red blood cell stimulating agents is prohibited by World Anti-Doping Agency (WADA).

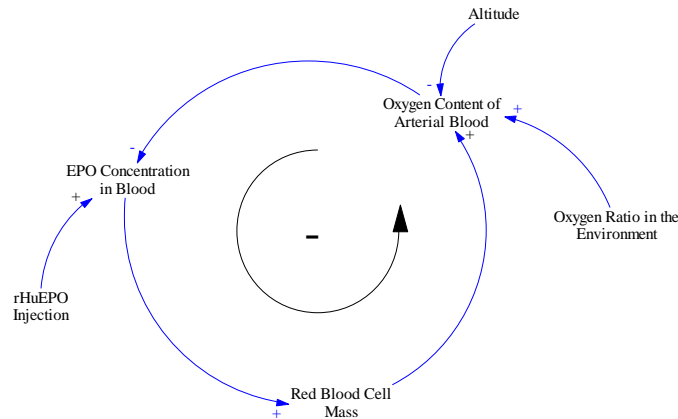


Figure 1: Simplified Causal Loop Diagram for EPO Regulation

Accordingly, EPO regulation structure and the pathways of rHuEPO in the body and their effects on red blood cells are included into the model (Figure 2). *EPO Concentration*, *Hemoglobin Concentration*, *Hematocrit* (red blood cell count) and *Reticulocyte Count* are the key variables that we are interested in.

We conduct several scenario analyses for the validation of the EPO regulation structure and rHuEPO pharmacodynamics. These scenario analyses include altitude training in various altitudes (an example can be seen in Figure 3) and rHuEPO intake of different dosages (an example can be seen in Figure 4). Based on these altitude and drug injection scenarios, we can conclude that our model is structurally and behaviourally valid.

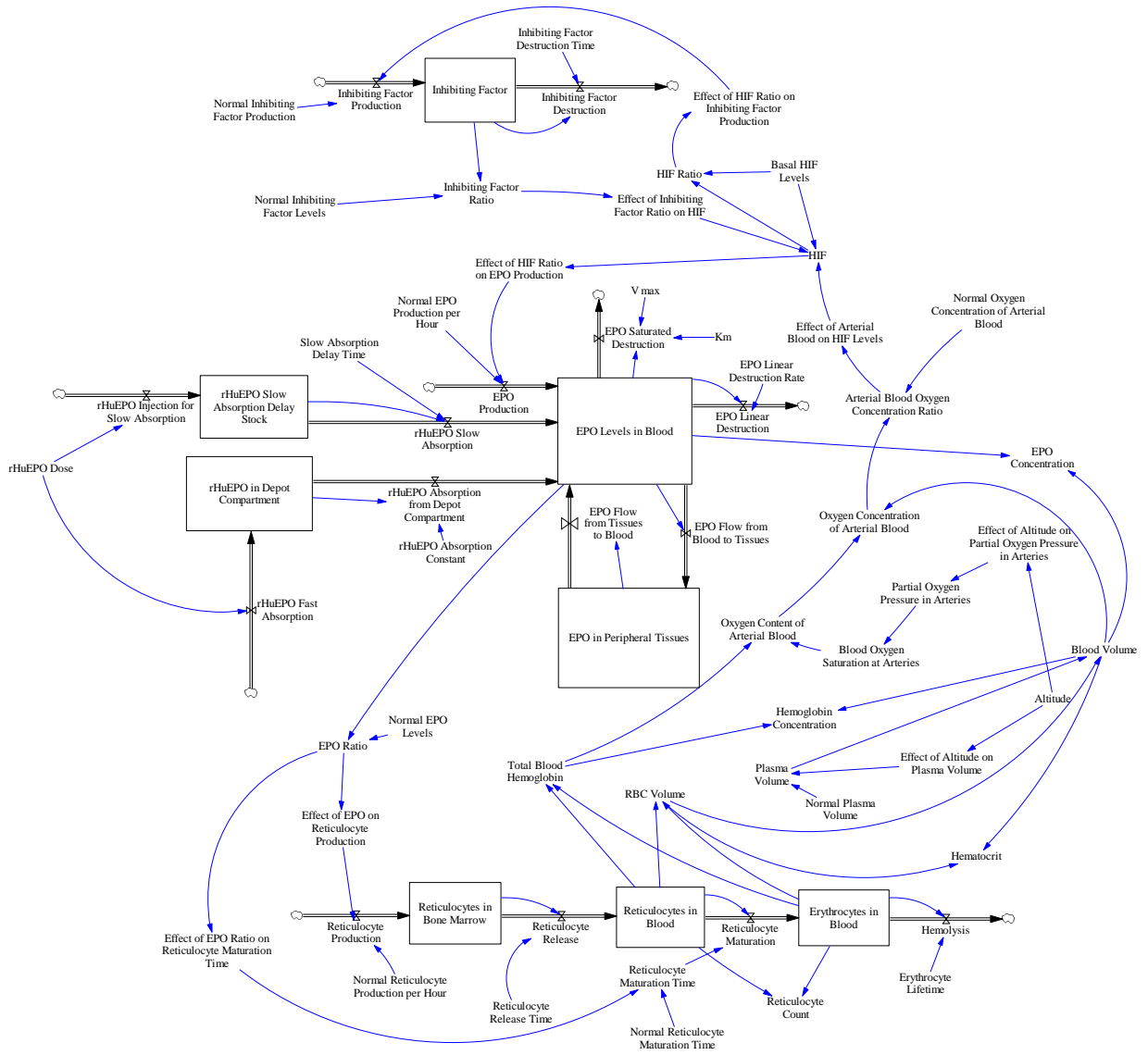


Figure 2: Simplified Model Structure

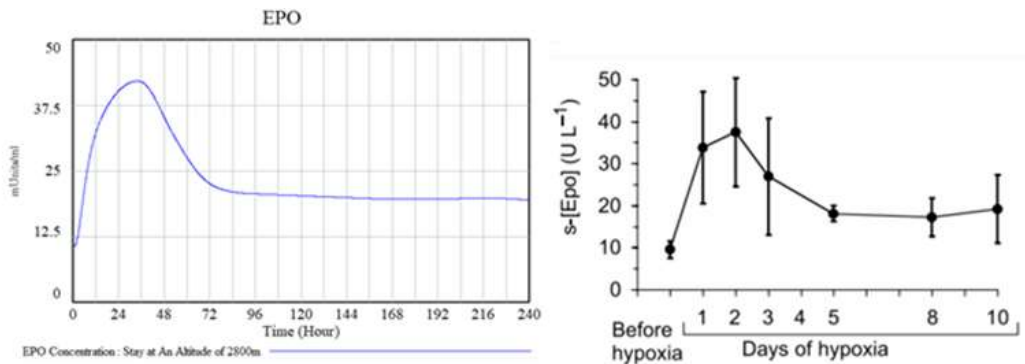


Figure 3: Model Generated Dynamics and Real Data for an Altitude Validation Scenario

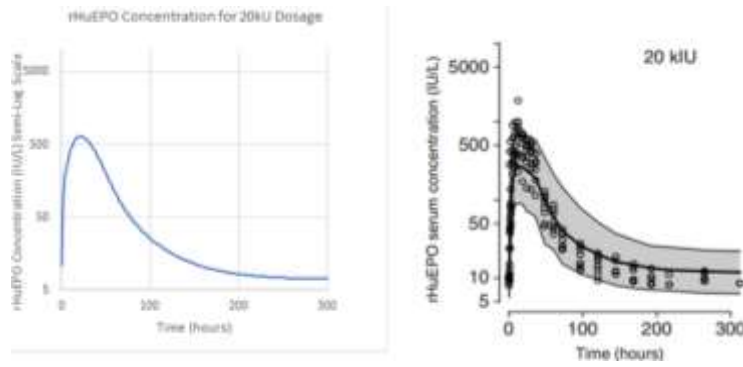


Figure 4: Model Generated Dynamics and Real Data for a rHuEPO Intake Scenario

The tests aiming to detect the usage of rHuEPO is mainly carried out by screening the various blood values affected by rHuEPO, which are the hematocrit value, hemoglobin concentration and reticulocyte count. Moreover, many athletes train at high altitudes to increase their red blood cell count and, thus, the oxygen capacity of their blood. Accordingly, we create three scenarios and analyse the resulting dynamics of EPO and relevant blood values: (1) rHuEPO usage; (2) altitude training; (3) altitude training together with rHuEPO usage. As an example, the dynamics of *EPO Concentration* and *Hematocrit* for the scenario involving the altitude training with rHuEPO usage and their comparison with dynamics from altitude training scenario is given in Figure 5.

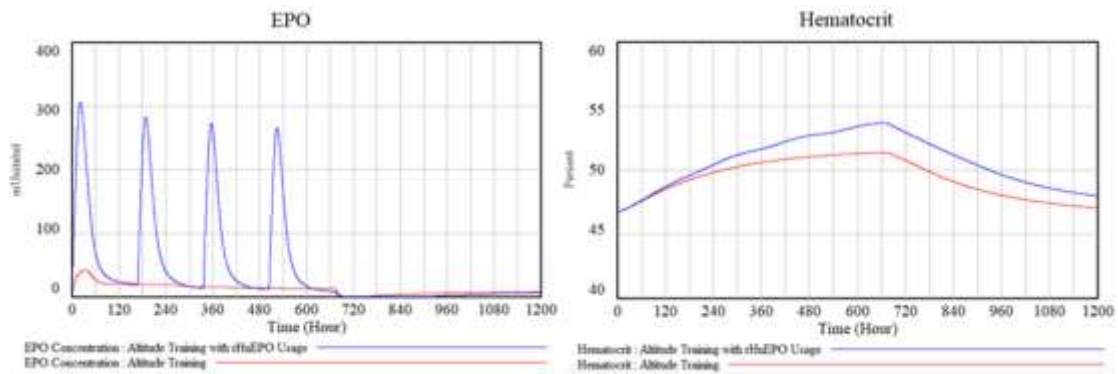


Figure 5: The Dynamics of *EPO Concentration* and *Hematocrit* for Altitude Training with rHuEPO Usage and Their Comparison with Altitude Training

According to our results, we suggest anti-doping agencies to create a new rule that states a boundary date before competition for blood testing. Moreover, in the altitude training with rHuEPO usage scenario, EPO levels stay low longer than regular altitude training. This information can be important in identifying an altitude trainer who is simultaneously using rHuEPO.

Our model can be modified to analyse the therapeutic effects of rHuEPO on anemic patients and to come up with personal optimal dosage regimens for the patients. As future work, the iron metabolism can be added to the model to see the limitations of red blood cell production and to find new markers for rHuEPO usage.

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