# QSP HW 1
# Modeling O2 Homeostasis

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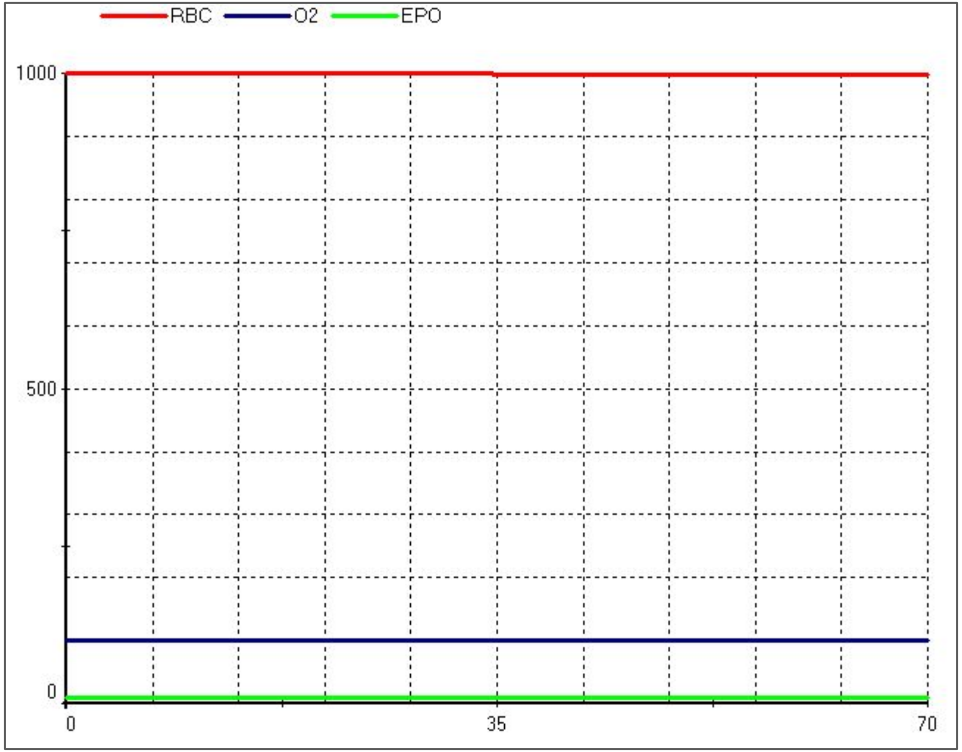
# O2 Homeostasis Model | **RBC = 1000 | O2 = 100 | EPO = 10**




Rate of change of concentration over time for the three variables, RBC, O2 and EPO, is zero. This appears to be the steady state of the model given by the following system of ODEs, initial conditions, and parameters.

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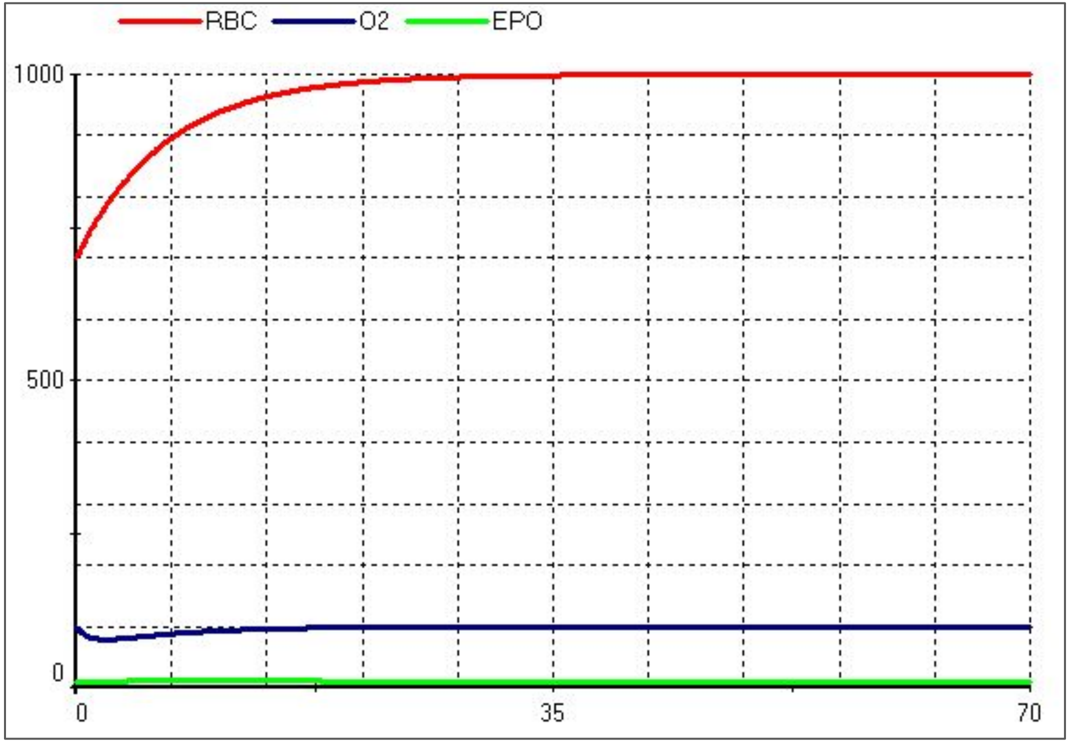
=====================================================================
Definition of differential equations
RBC' = a1 * SC * (1 + 0.5 * EPO^4 / (2^4 + EPO^4)) -  b1 * RBC
O2'  = (a2 * RBC) - (b2 * O2)
EPO' = (a3 * O2^g3) -  (b3 * EPO)
=====================================================================
Initial values, one each
RBC = 1000
O2 = 100
EPO = 10
=====================================================================
Definition of parameters
a1 = .1
b1 = .15
g3 = -1
a2 = .1
b2 = 1.0
SC = 1000
a3 = 100
b3 = .1
```

# Effect of Decreasing Initial Conditions | **[RBC] = 700**

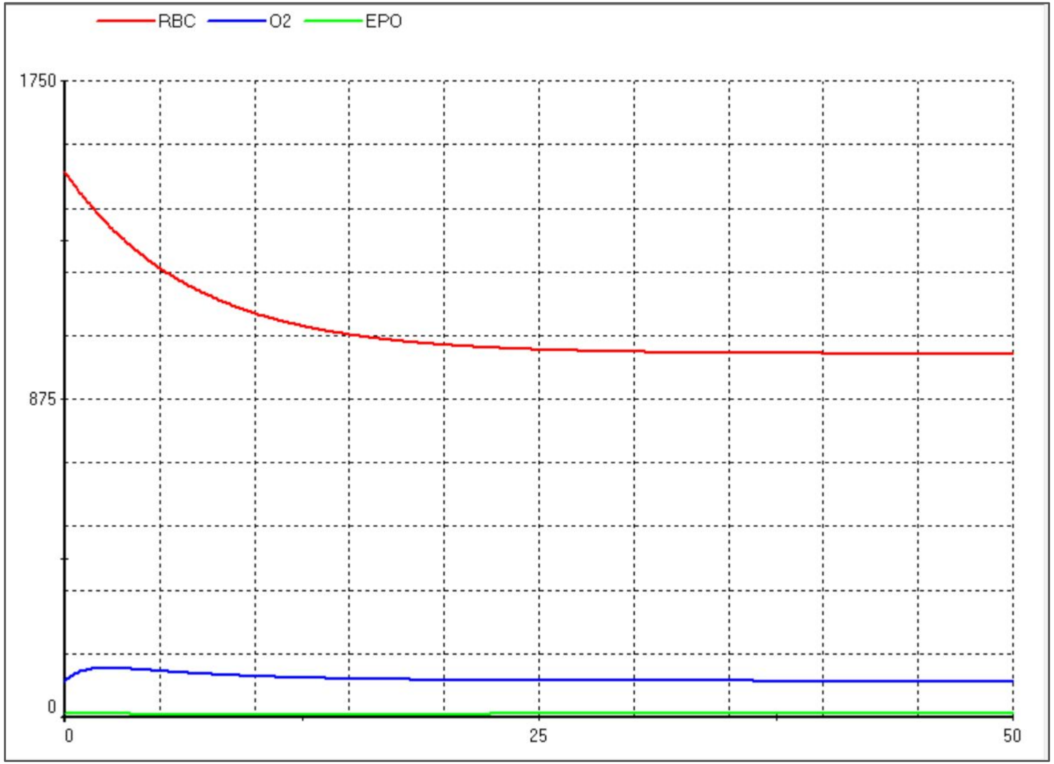



Rate of change of RBC is positive, then rate decreases as [RBC] reaches homeostatic state of 1000 at approximately 43 hrs and slope plateaus.

[O2] is lowest at 2.7 hrs and [EPO] highest at 8.7 hrs according to tabular results. Rate of change of O2 is negative for approximately 3 hrs before slope increases back to homeostatic state of 100.

Rate of change of EPO increases slightly (not visible in graph) with highest [EPO] = 11.0537 before returning to homeostatic state of 10.

# Effect of Increasing Initial Conditions | **[RBC] = 1500**



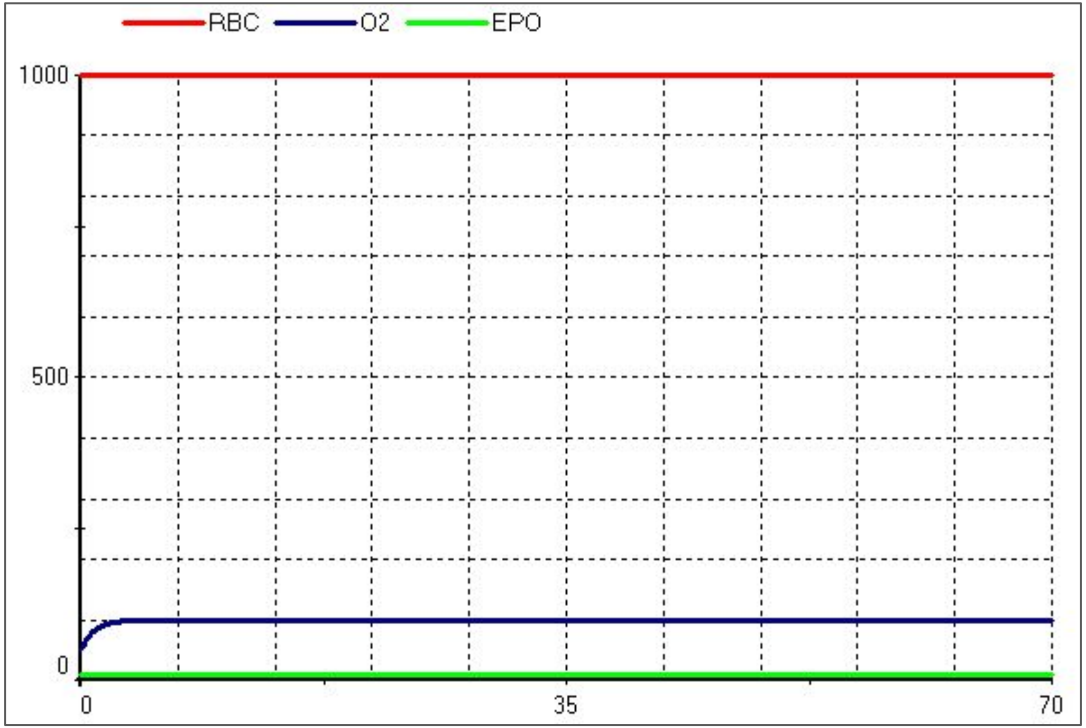

The concentration of RBC decreases and returns to the original homeostatic state of 1000.

The concentration of O2 increases initially then decreases to return to the original homeostatic state of 100.

The concentration of EPO decreases slightly before returning to original homeostatic state of 10.

All return to original homeostatic state around 39 hours after change.

# Effect of Decreasing Initial Conditions | **[O2] = 50**

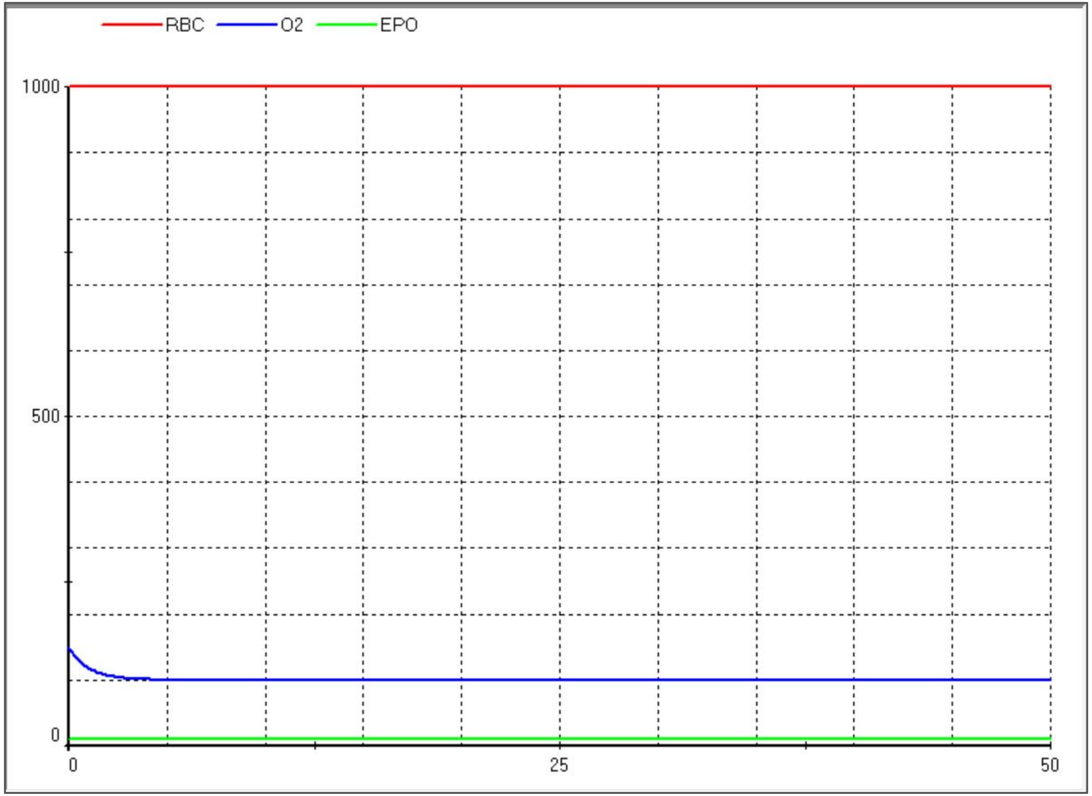



Rate of change of O2 is positive until [O2] reaches homeostatic state of 100 at approximately 15 hrs according to tabular results.

[EPO] increases slightly as compared to homeostatic state of 10 according to tabular results.

[RBC] decreases slightly as compared to homeostatic state of 100 according to tabular results.

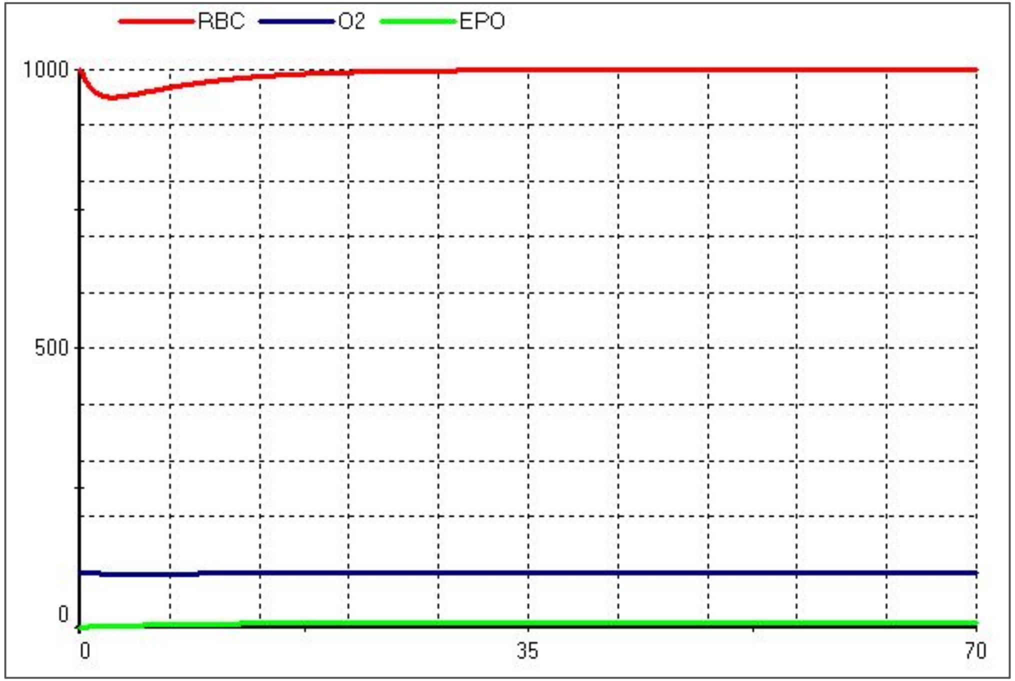
# Effect of Increasing Initial Conditions | **[O2] = 150**




Concentration of RBC and EPO are not really affected by an increase in O2 concentration.

O2 concentration immediately starts to decrease and returns to original homeostatic state of 100 within 7 hours.

# Effect of Decreasing Initial Conditions | **[EPO] = 1**

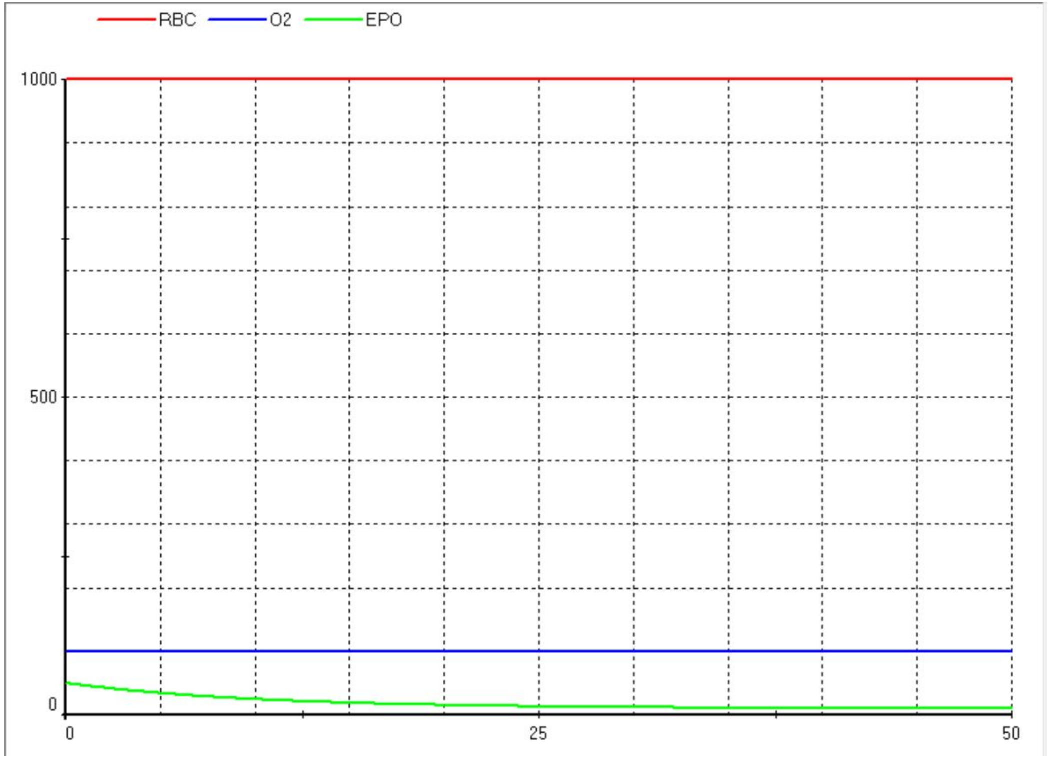



[RBC] decreased immediately with lowest concentration of 950.136 occurring at 2.6 hrs before steadily increasing and returning to homeostatic state of 1000.

[O2] decreased with lowest concentration of 95.381 occurring at 4 hrs before increasing back to homeostatic state of 100.

Rate of change of [EPO] is positive until approximately 28 hrs before plateauing with a new slightly higher homeostatic state.

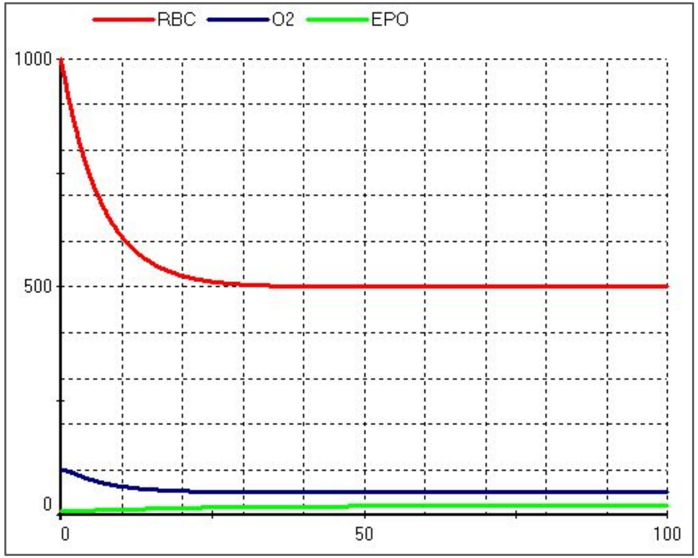
# Effect of Increasing Initial Conditions | **[EPO] = 50**

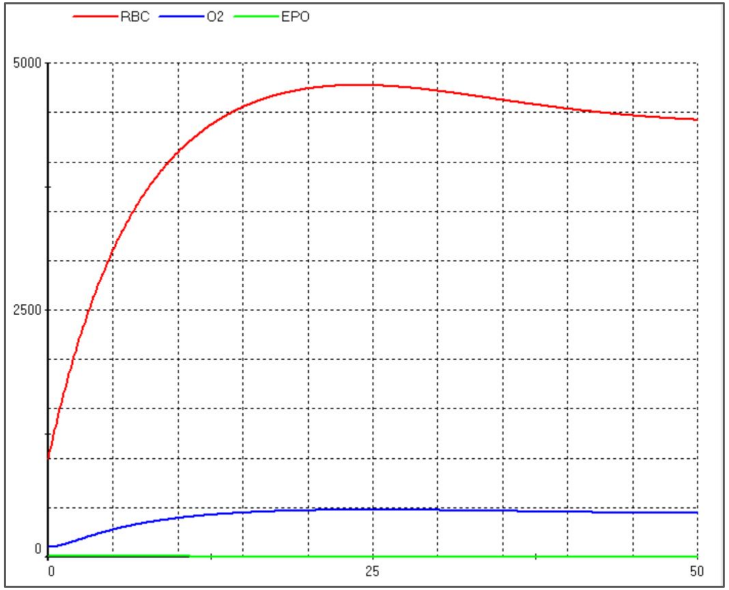



The concentrations of RBC and O2 are not affected by the increase in EPO concentration.

The concentration of EPO immediately starts to decrease and slowly returns to original homeostatic state of 10. The return to the original state takes around 60 hours.

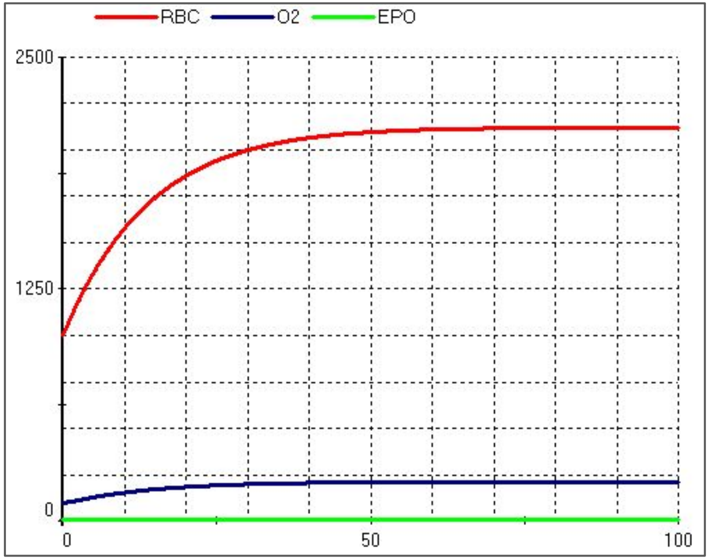
# Effect of Changing Parameters | **A1 = 0.05 (left) | A1 = 0.5 (right)**

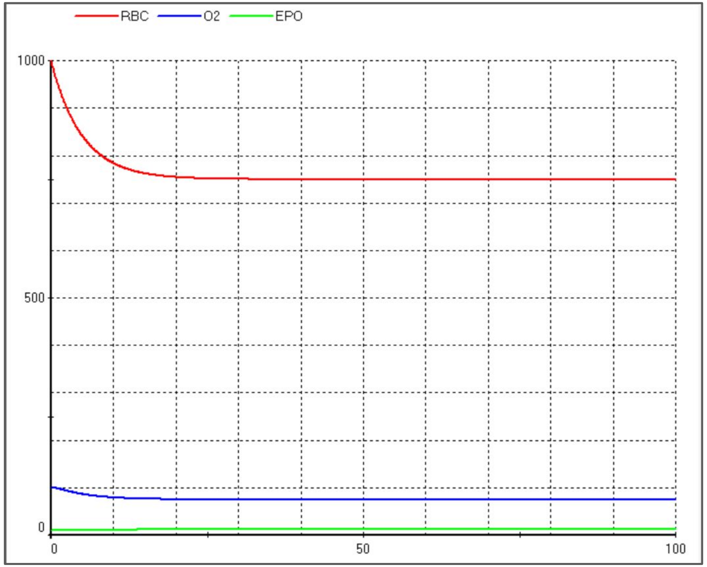



| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | Increase, peak, decrease | Increase, peak, decrease | Decrease | RBC & O2 new higher equilibrium while EPO lower equilibrium |
| Decrease Parameter (left graph) | Decrease, plateau | Decrease, plateau | Increase | RBC & O2 lower equilibrium while EPO higher equilibrium |

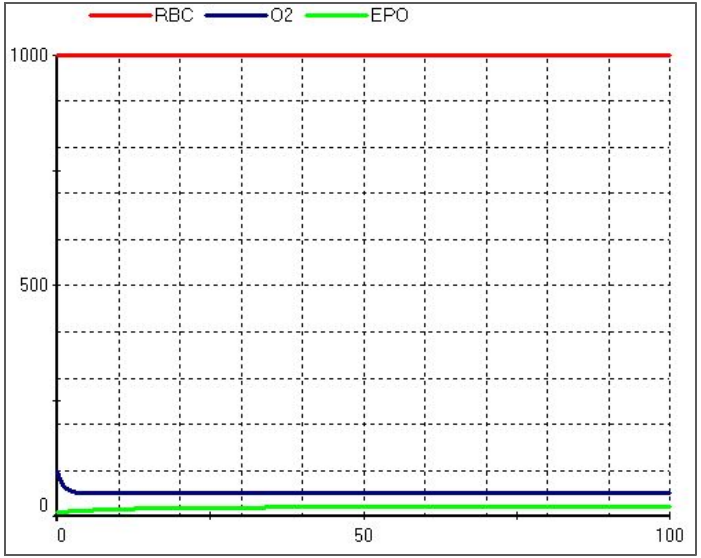
# Effect of Changing Parameters | **B1 = 0.07 (left) | B1 = 0.2 (right)**

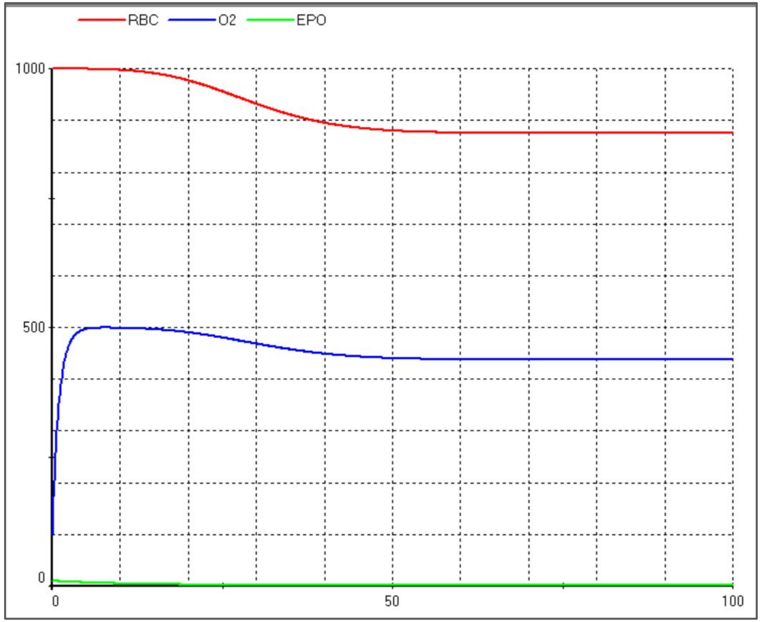



| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | Decrease | Decrease | Increase | RBC & O2 lower equilibrium while EPO higher Equilibrium |
| Decrease Parameter (left graph) | Increase | Increase | Decrease | RBC & O2 higher equilibrium while EPO lower equilibrium |

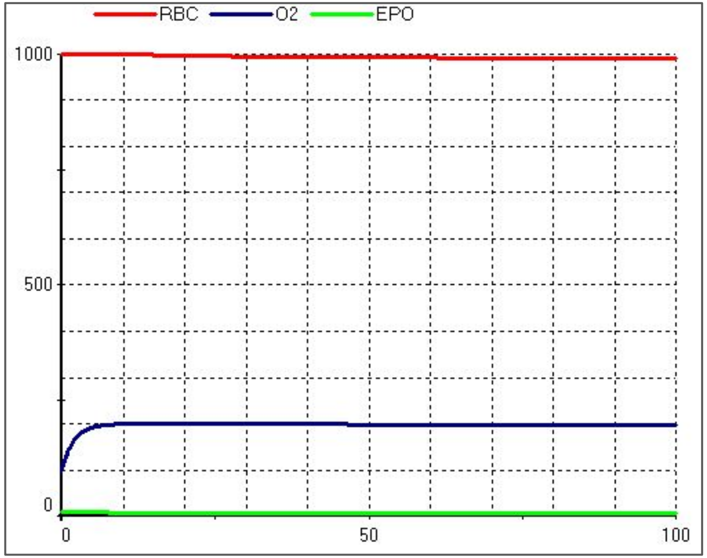
# Effect of Changing Parameters | **A2 = 0.05 (left) | A2 = 0.5 (right)**

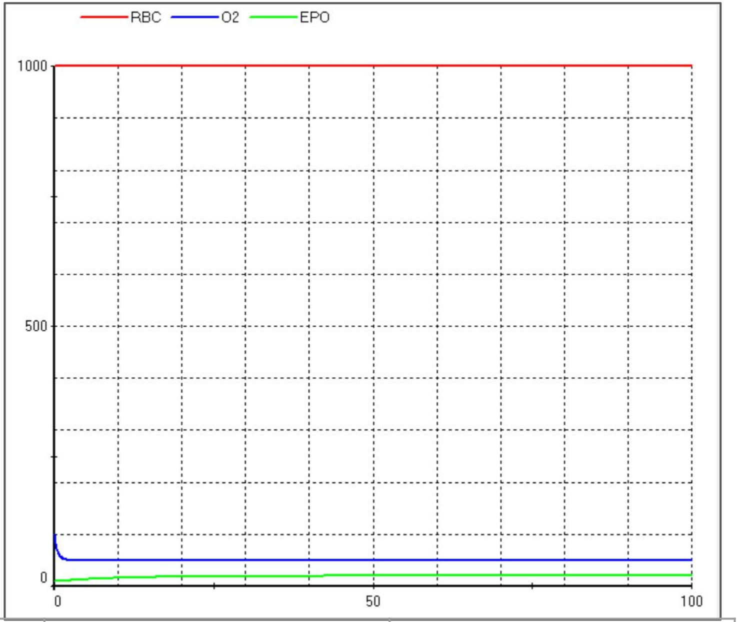



| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | Decrease | Increase | Decrease | RBC and EPO have lower equilibrium, O2 has higher equilibrium |
| Decrease Parameter (left graph) | No change | Decrease, plateau | Increase, plateau | O2 has lower equilibrium, EPO has higher equilibrium |

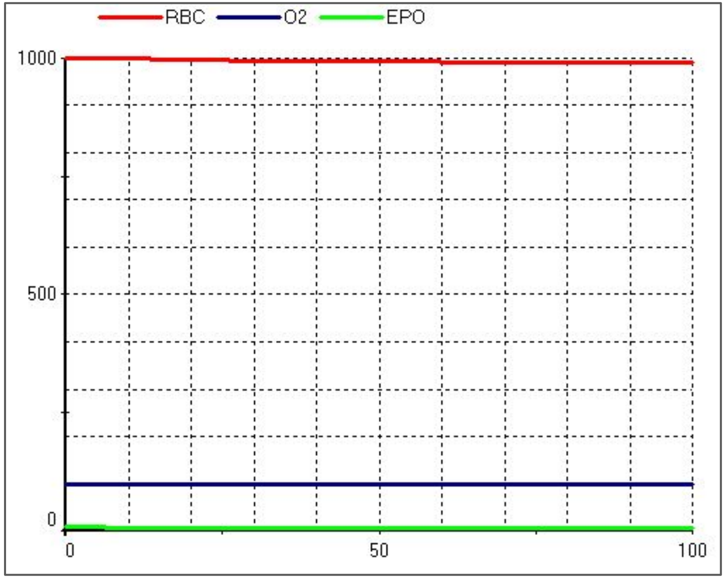
# Effect of Changing Parameters | **B2 = 0.5 (left) | B2 = 2.0 (right)**

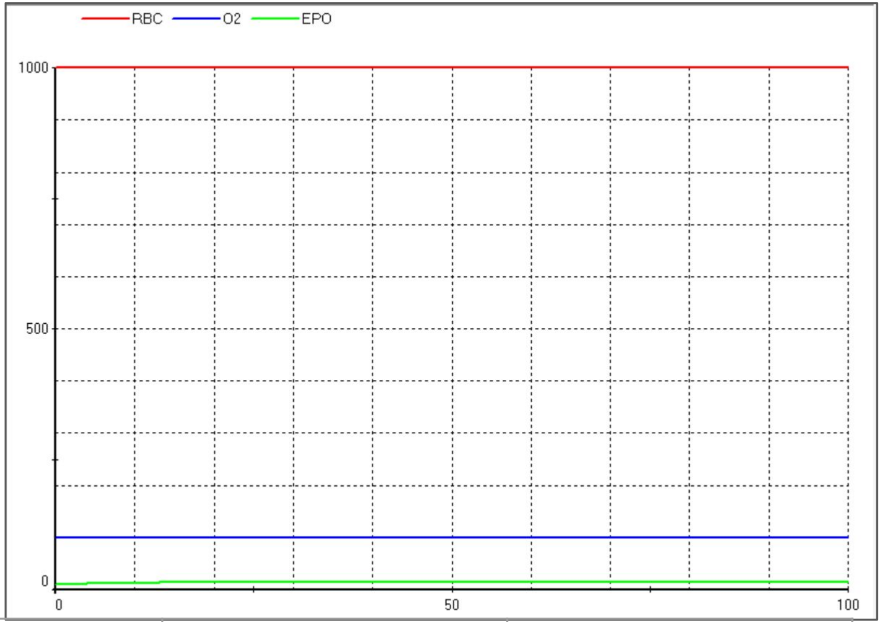



| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | No Change | Decrease | Increase | O2 has lower equilibrium while EPO has higher equilibrium |
| Decrease Parameter (left graph) | No Change | Increase, plateau | Decrease | O2 has higher equilibrium while EPO has lower equilibrium |

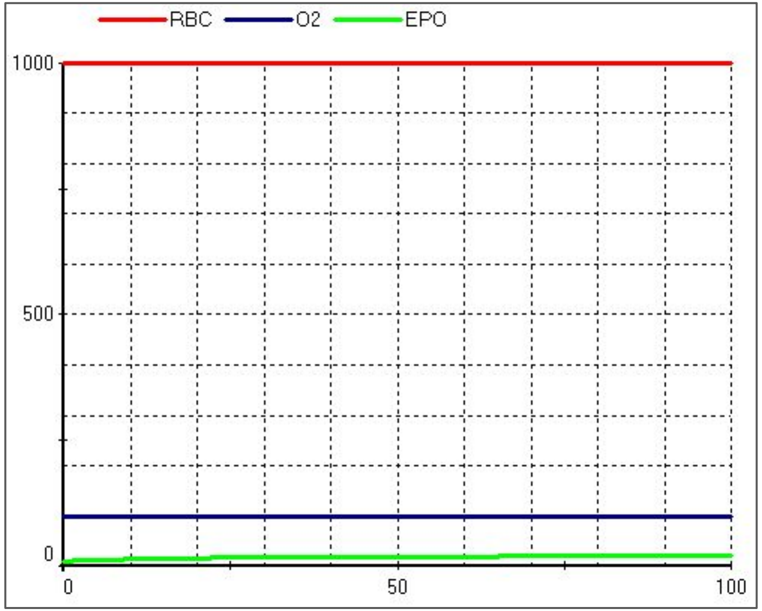
# Effect of Changing Parameters | **A3 = 50 (left) | A3 = 150 (right)**

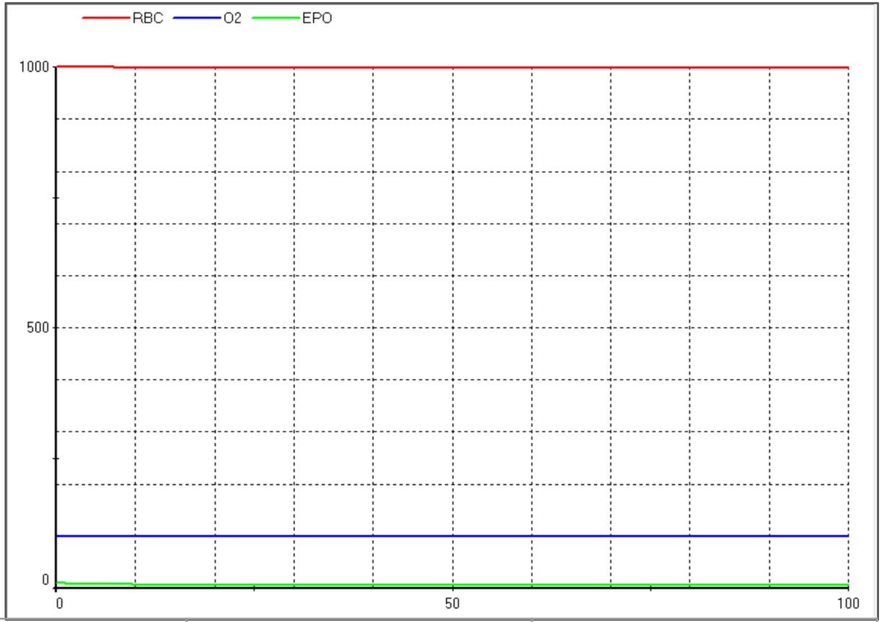



| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | No Change | No Change | Increase | EPO has higher equilibrium |
| Decrease Parameter (left graph) | No Change | No Change | Decrease | EPO has lower equilibrium |

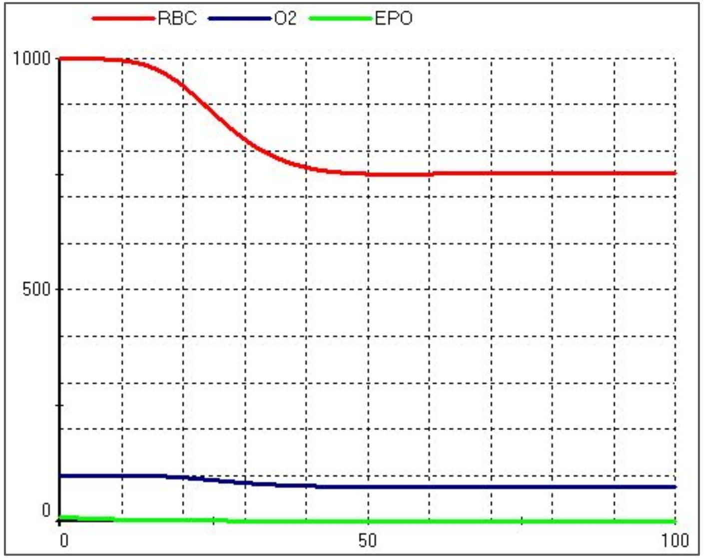
# Effect of Changing Parameters | **B3 = 0.05 (left) | B3 = 0.15 (right)**

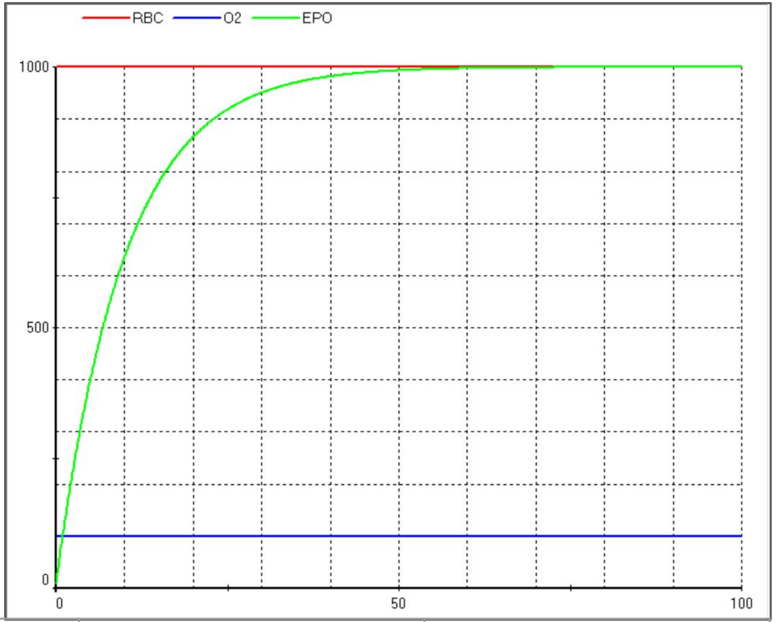



| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | No Change | No Change | Decrease | EPO has lower equilibrium |
| Decrease Parameter (left graph) | No Change | No Change | Increase | EPO has higher equilibrium |

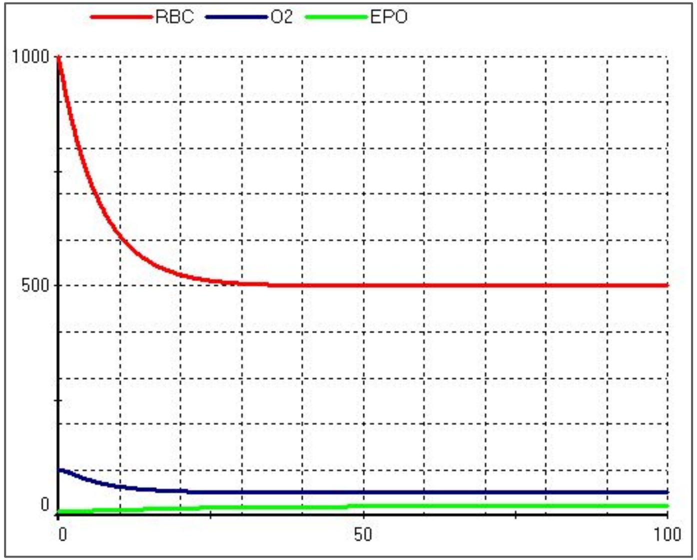
# Effect of Changing Parameters | **G3 = -1.5 (left) | G3 = 0 (right)**

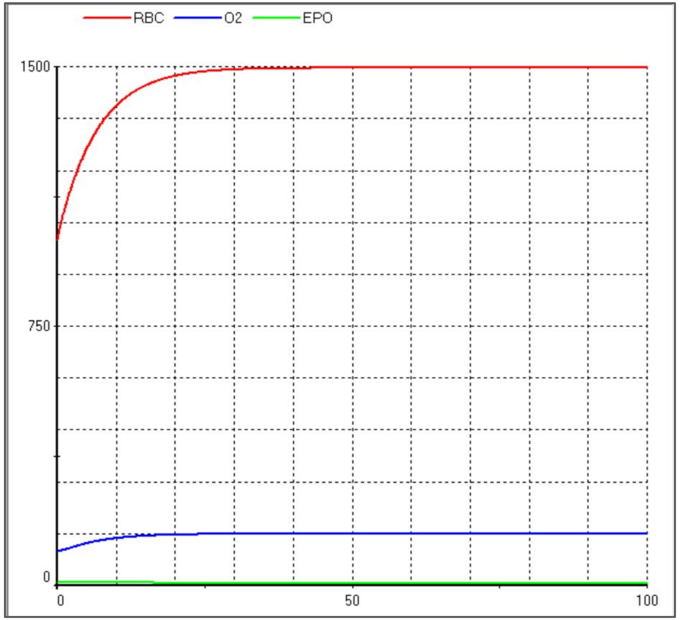



| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | No Change | No Change | Increase | Only EPO has new higher equilibrium |
| Decrease Parameter (left graph) | Decrease, plateau | Decrease, plateau | Decrease | RBC, O2, & EPO have lower equilibriums |

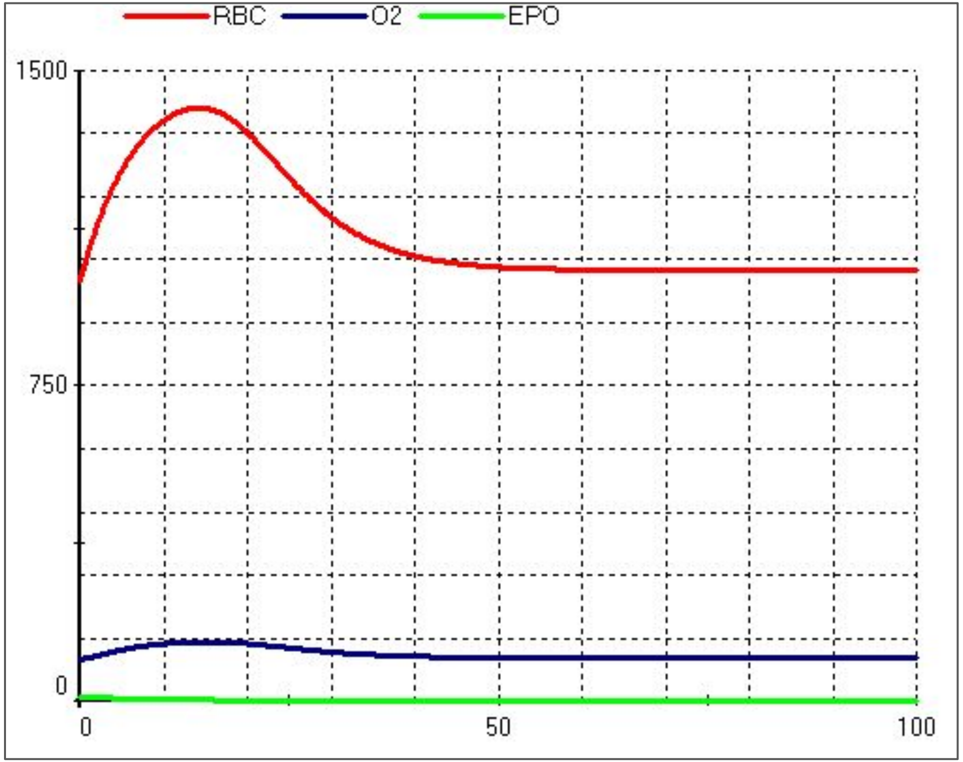
# Effect of Changing Parameters | **SC = 500 (left) | SC = 1500 (right)**




| | RBC | O2 | EPO | New Equilibrium |
|---|---|---|---|---|
| Increase Parameter (right graph) | Increase | Increase | Decrease | RBC & O2 have higher equilibrium while EPO has lower equilibrium |
| Decrease Parameter (left graph) | Sharp decrease, plateau | Decrease, plateau | Increase | RBC & O2 have lower equilibrium while EPO has higher equilibrium |

# Combined Changes - **Case 1: Low G3 = -1.5 & High SC = 1500**

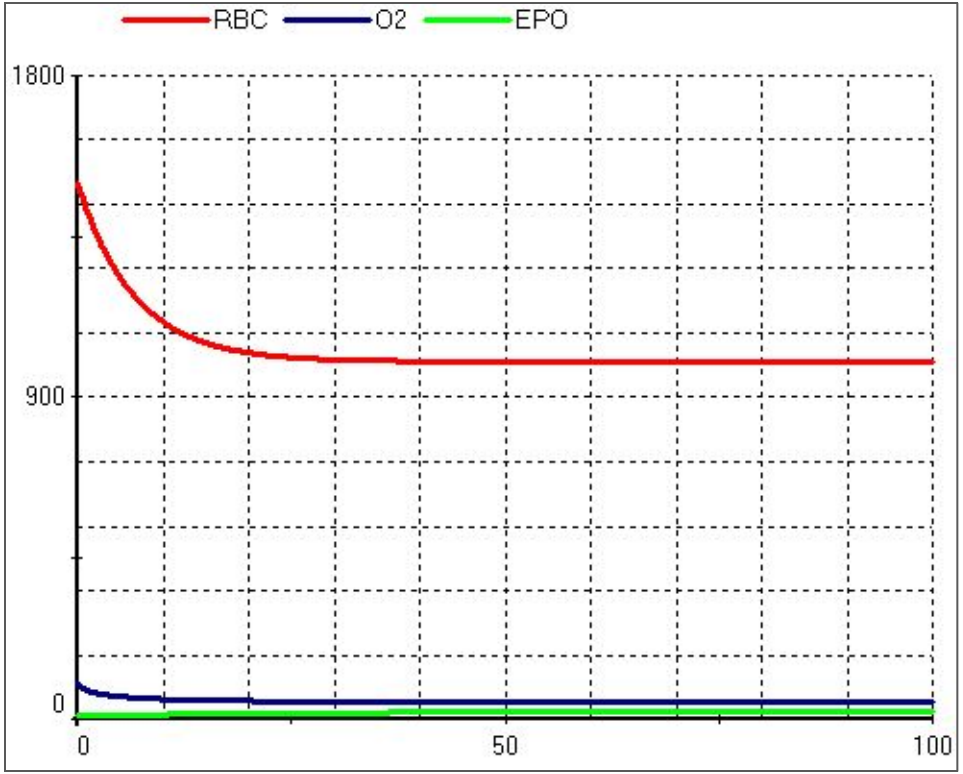



[RBC] increases steeply before peaking at concentration of 1410 at 15 hrs and then rate of change is negative before plateauing at homeostatic level of 1000 at approximately 45 hrs.

[O2] increases slowly and peaks at 140 at 15 hrs before returning to homeostatic state of 100.

[EPO] decreases to new homeostatic state of 1 (as compared to initial condition of 10) according to tabular results.

# Combined Changes - **Case 2: Low A2 = 0.05 & High RBC = 1500**

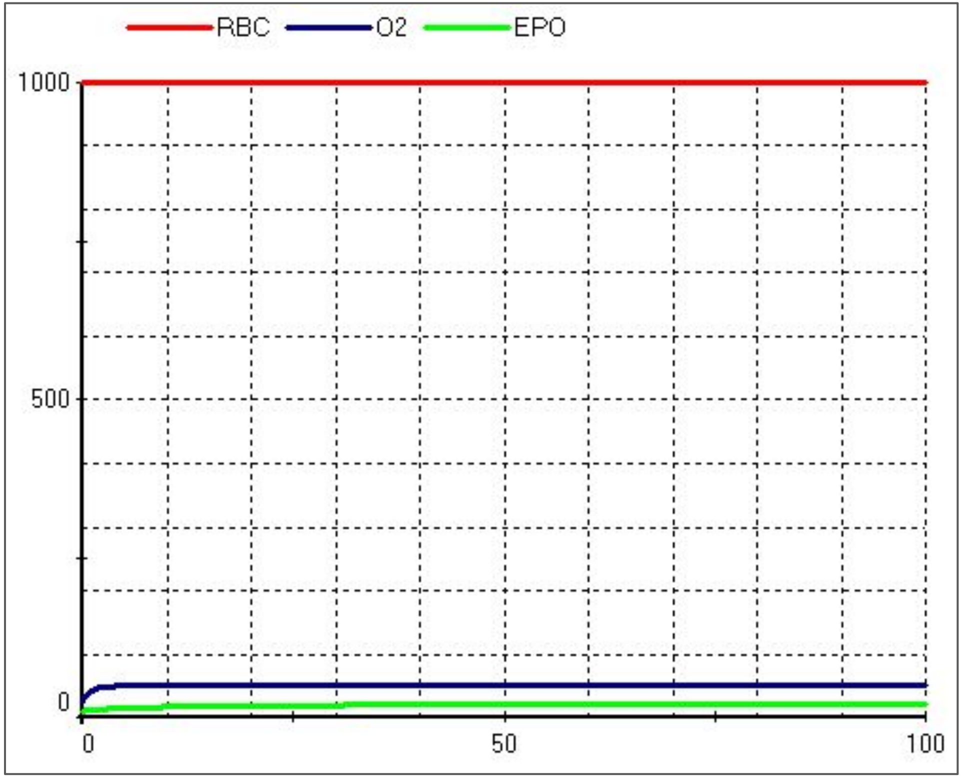



[RBC] decreases steadily until returning to homeostatic state of 1000 at approximately 30 hrs.

[O2] decreases until reaching new homeostatic state of 50 at approximately 30 hrs.

[EPO] increases and reaches new homeostatic state of 19 at approximately 30 hrs.

# Combined Changes - **Case 3 | Low A2 = 0.05 & Low O2 = 25**

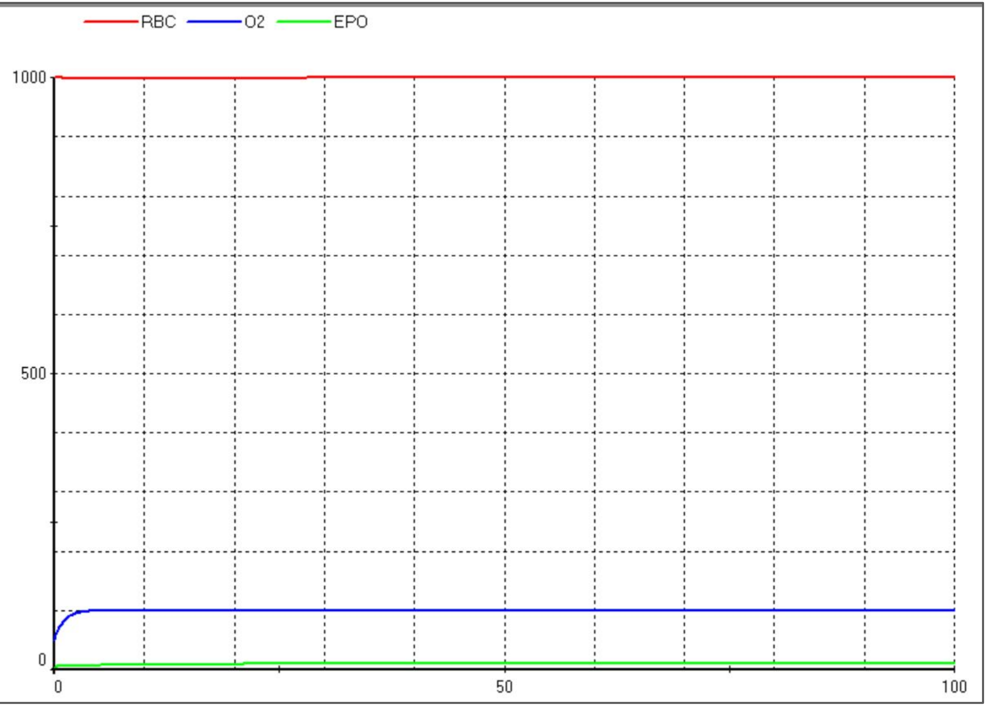



[RBC] has no change and remains at homeostatic level of 100.

[O2] increases until reaching new homeostatic level of 50 at approximately 4 hrs.

[EPO] increases and reaches new baseline of 20 at approximately 95 hrs.

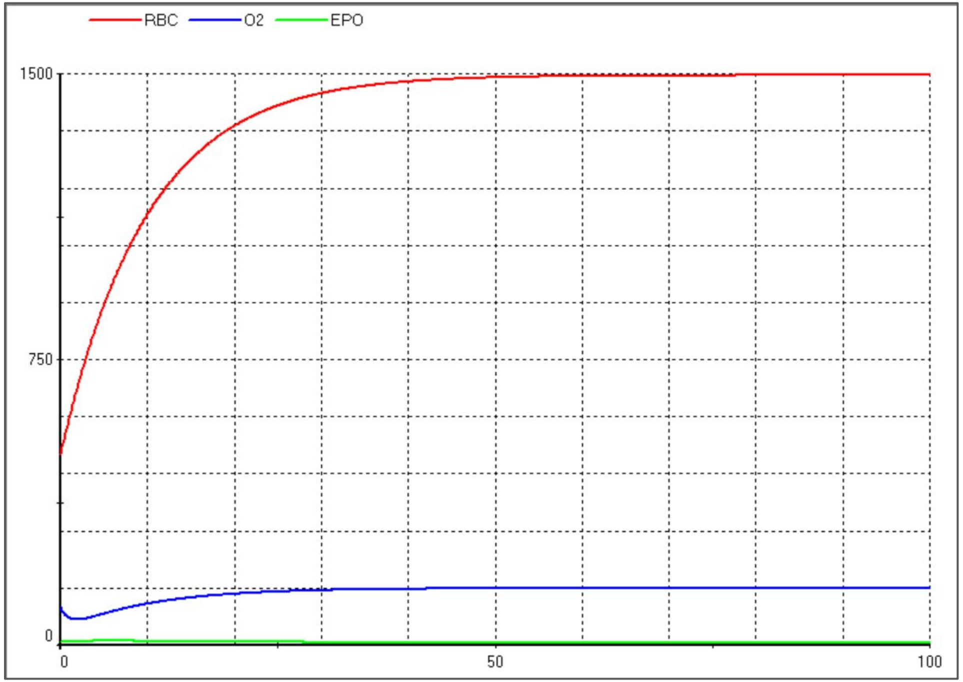
# Combined Changes - **Case 4: Low [O2] = 50 & Low [EPO] = 5**




In this situation RBC concentration is not affected.

The concentrations of O2 and EPO both increase until they return to the original homeostatic state of 100 and 10 respectively. This process takes around 37 hours.

# Combined Changes - **Case 5: Low [RBC] = 500 & Low B1 = 0.1**

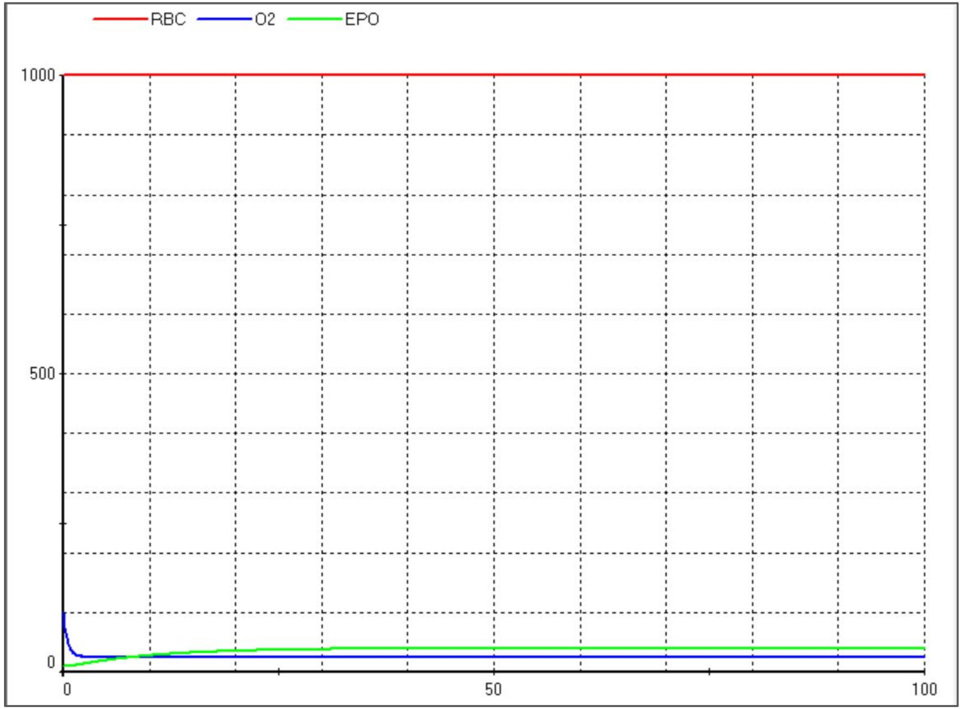



In this situation the concentration of RBC immediately starts to increase to a new equilibrium of 1500, where it remains as a new homeostatic state.

The concentration of O2 initially decreases for around 2 hours then increases until it reaches a new homeostatic state of 150.

The concentration of EPO increases very slightly initially before decreasing to a new lower equilibrium state of 6.7.

# Combined Changes - **Case 6: Low A2 = 0.05 & High B2 = 2.0**

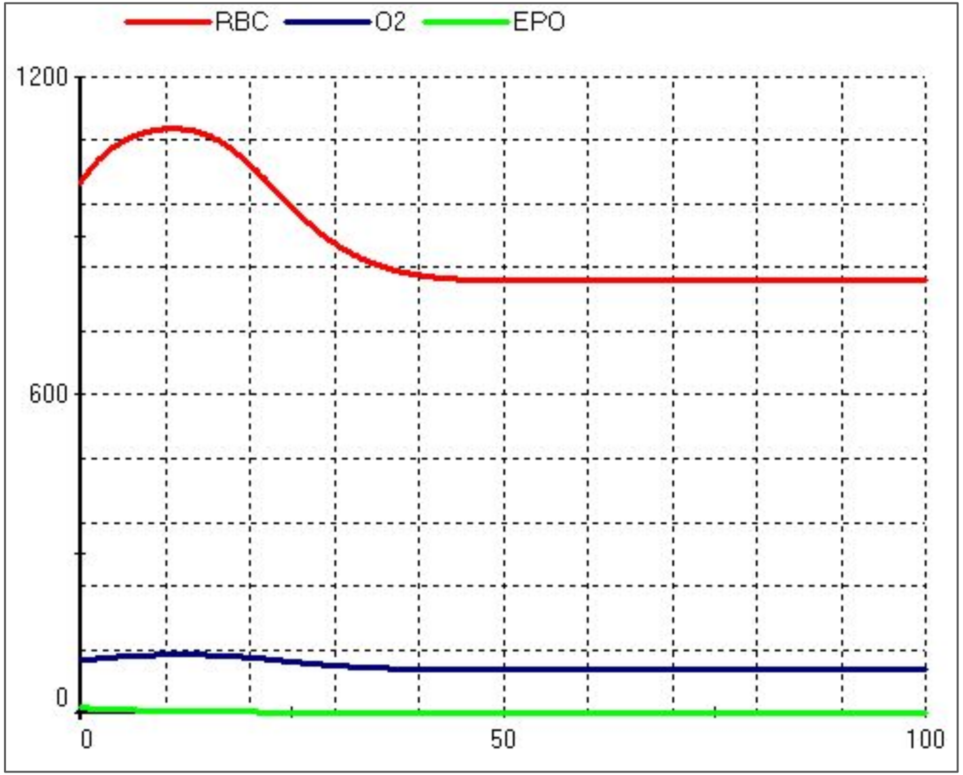



In this situation the concentration of RBC is not affected.

The concentration of O2 decreases to a new equilibrium of 25 within 5 hours.

The concentration of EPO increases to a new equilibrium of 39 within 35 hours.

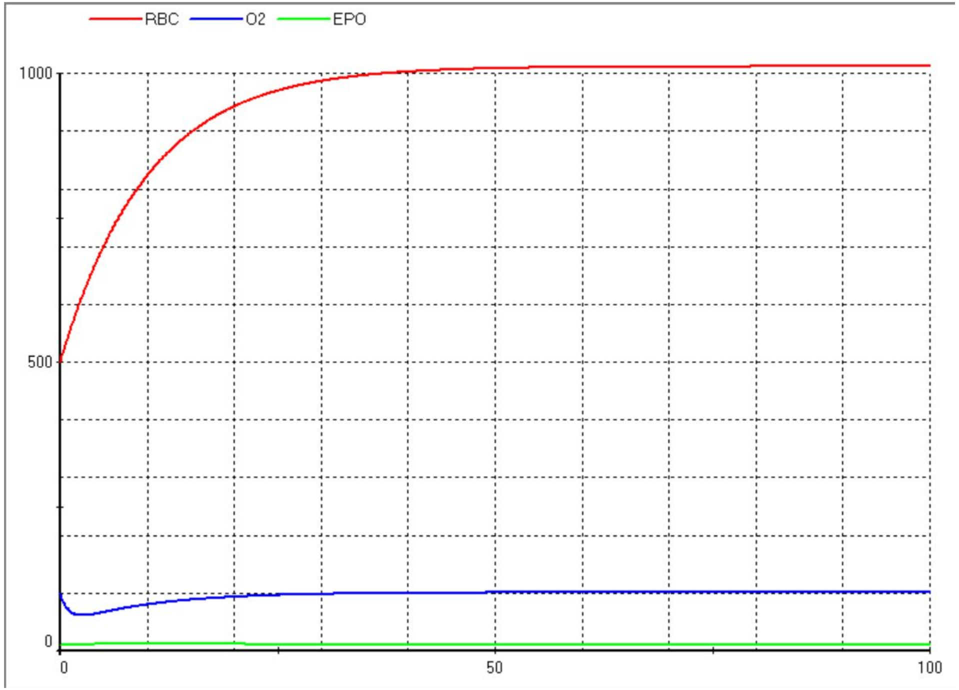
# Additional Trial of Case 1: **Low G3 = -1.5 & High SC = 1500**




To minimize the overshoot of [RBC] in Case 1 (g3 = -1.5 & SC = 1500), the b1 parameter was increased to 0.2. This parameter corresponds to the degradation/loss of RBC. It was chosen on the understanding that if the body depletes more RBCs than the high stem cell count would not cause a sharp increase in [RBC] as simulated in Case 1.

This change minimized the overshoot found in Case 1, and it also sped up the return of [RBC] to its homeostatic level of 1000 by 22 hrs whereas in Case 1, [RBC] returned to baseline at approximately 45 hrs.

# Additional Trials of Case 5: **Low [RBC] = 500 & Low B1 = 0.1**




In this situation we observe a final homeostatic state of RBC at 1500, O2 at 150, and EPO at 6.7. To return to the original homeostatic state we need to find a way to decrease RBC and O2 and increase EPO.

In the graph to the left, I decreased the concentration of SC to 675, which resulted in RBC, O2, and EPO returning to their original homeostatic state of 1000, 100, 10 respectively. This took approximately 37.5 hours.

Adjusting SC did not result in large over/undershoots when approaching the original homeostatic state. The time it took to get to this state was also not very long.

# Discussion

**Does system always return to the same homeostatic state?**

This depends on the changes made. In some cases, such as: Case 4, or when only the initial conditions are altered the system will return to the original homeostatic state. In other cases, such as when the parameters are changed, the system will not return to the original homeostatic state, but will find a new one.

**If so, how long does it take?**

The return to the original homeostatic state depends on the conditions/parameters changed. In some cases it could be very quick to return to the original state. When O2 concentration was increased to 150, the return to baseline took only 7 hours. However, when increasing the concentration of EPO to 50, the return to baseline took closer to 60 hours.

**If not, what happens to the system?**

If the system does not return to the original homeostatic state, a new homeostatic state is reached. For example, when the parameter $a1$ was increased, the new equilibrium reached resulted in a higher value for RBC & O2, while a lower value for EPO. When $a1$ is decreased, the new equilibrium resulted in a lower value for RBC & O2 while EPO has a higher value.

# Discussion continued

**Can you minimize overshoots/undershoots?**

Based on our studies of the different simulations of this model there are a few methods that can limit over/undershoots. The best method involves balancing the feedback mechanisms found in the model. The notable feedback mechanisms we have observed:

- O2 is a negative feedback regulator for EPO.
- EPO is a positive feedback regulator for RBC.
- RBC is a positive feedback regulator for O2.

Depending on the system we are observing we can use the feedback mechanisms to provide more stability to the system. For some of our parameters:

- A1 is associated with SC being converted to RBC (RBC production rate), altering this parameter can either reduce or increase the available pool of RBCs. This is useful if we are noticing fluctuations in RBCs in the system.
- B1 is associated with degradation of RBCs, if we notice excessive overshoots of RBCs we could increase b1 and vice versa if we observe undershoots of RBCs.
- B2 is associated with use of O2 in the tissues (O2 degradation), if we notice undershoots of O2 we can decrease b2 and vice versa if we notice overshoots of O2.
- B3 is associated with degradation of EPO, increasing this value will lead to less EPO in the system and likewise an increase will allow for more EPO in the system.

**Can you speed up the return to homeostasis?**

Playing with these values can help us determine a faster or slower return to homeostasis. In the case of undershoots we could decrease degradation rates so we can potentially allow for a faster return to homeostasis. This would allow for a slower loss of RBC/O2/EPO and allow the system time to catch up to the perturbations. Likewise, if we are experiencing overshoots we can increase degradation times to help the system eliminate the excess concentrations faster and return to homeostasis.