CytoCopasi: A Chemical Systems Biology Target and Drug Discovery Visual Data Analytics Platform

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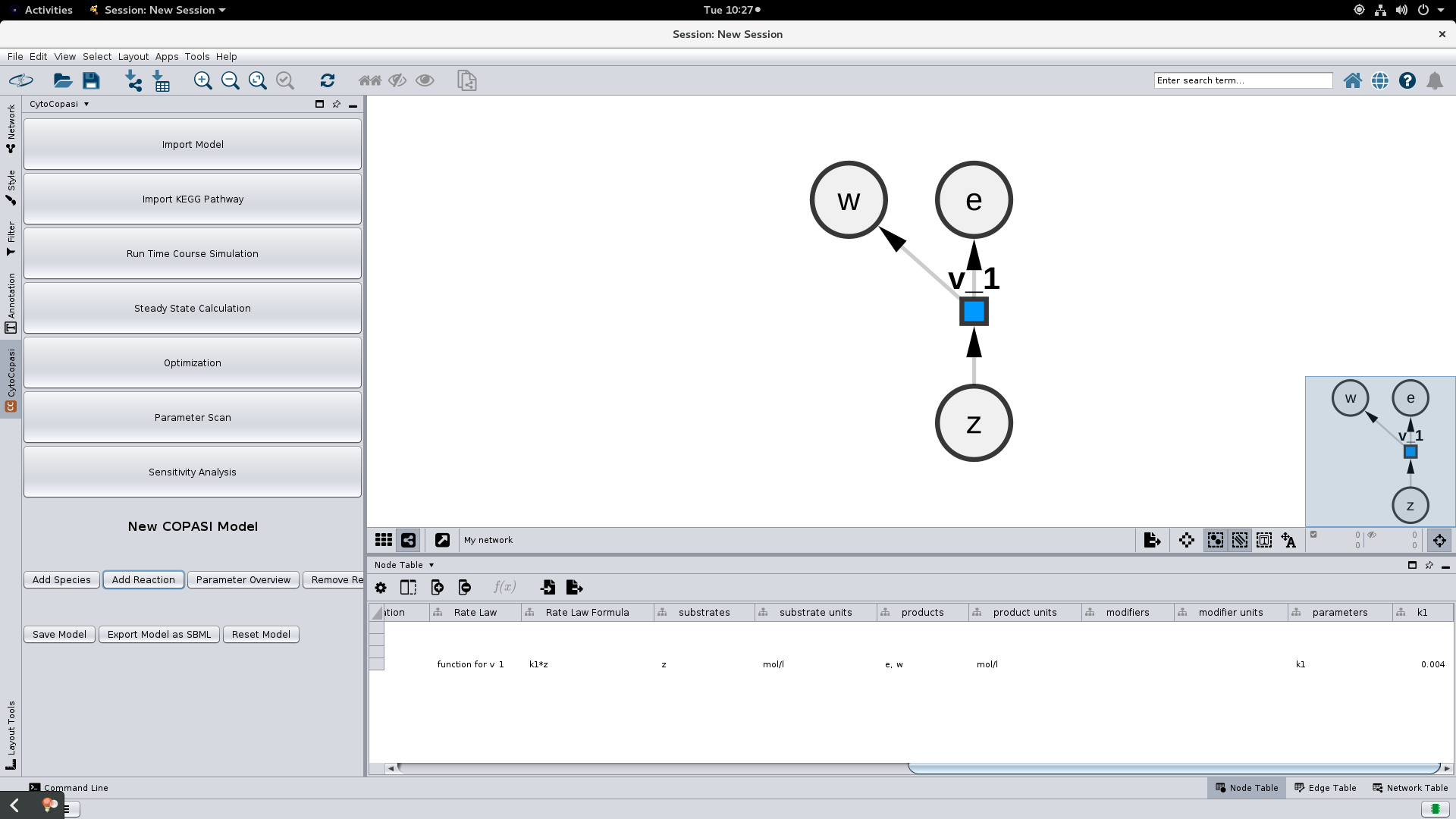
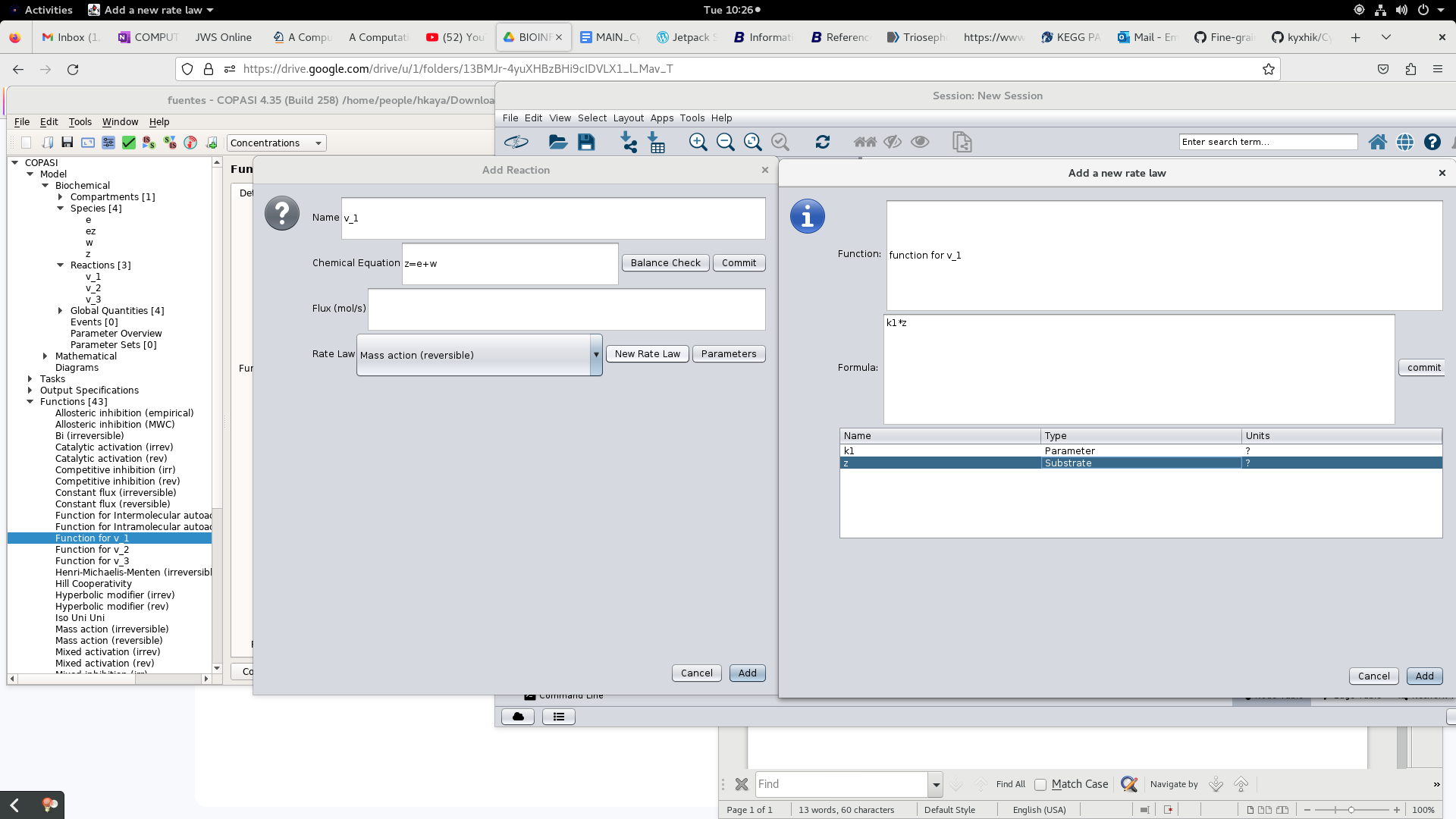
## 1- Step-by-step Model Construction for Fuentes et al. [1] (BIOMD0000000092)

Time Unit:s; Volume Unit: l ; Quantity Unit: mol

**Reaction v\_1**

z=e+w

Function for v\_1:

k1\*z ; k1 = 0.004 l/s

**Figure S1**: The reaction specifics for v\_1 entered into CytoCopasi and the resulting network view

**Reaction: v\_2**

e+z=ez

Function for v\_2

k21\*e\*z-k22\*ez

k21 = 1000 l2/(mol\*s)

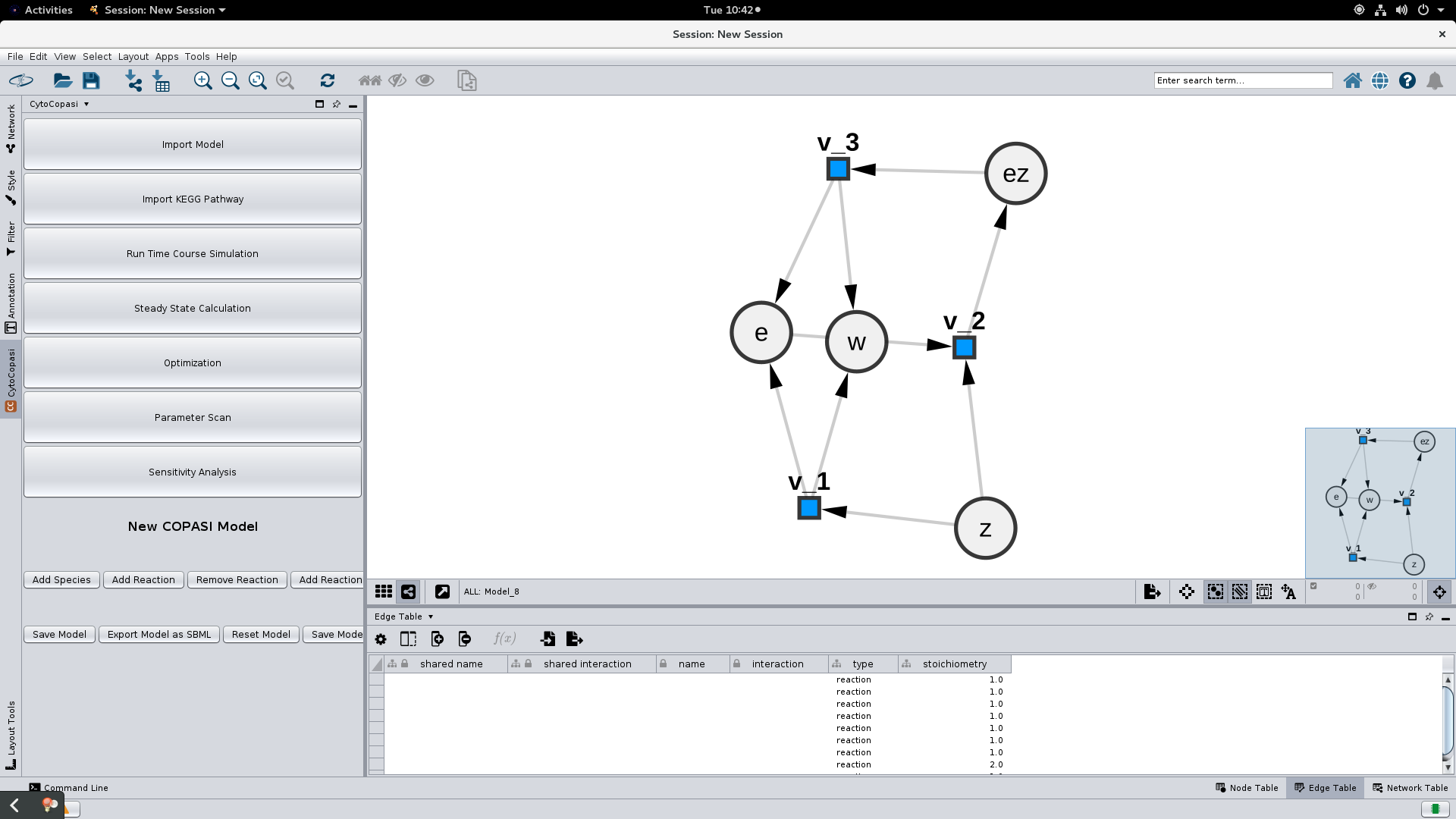
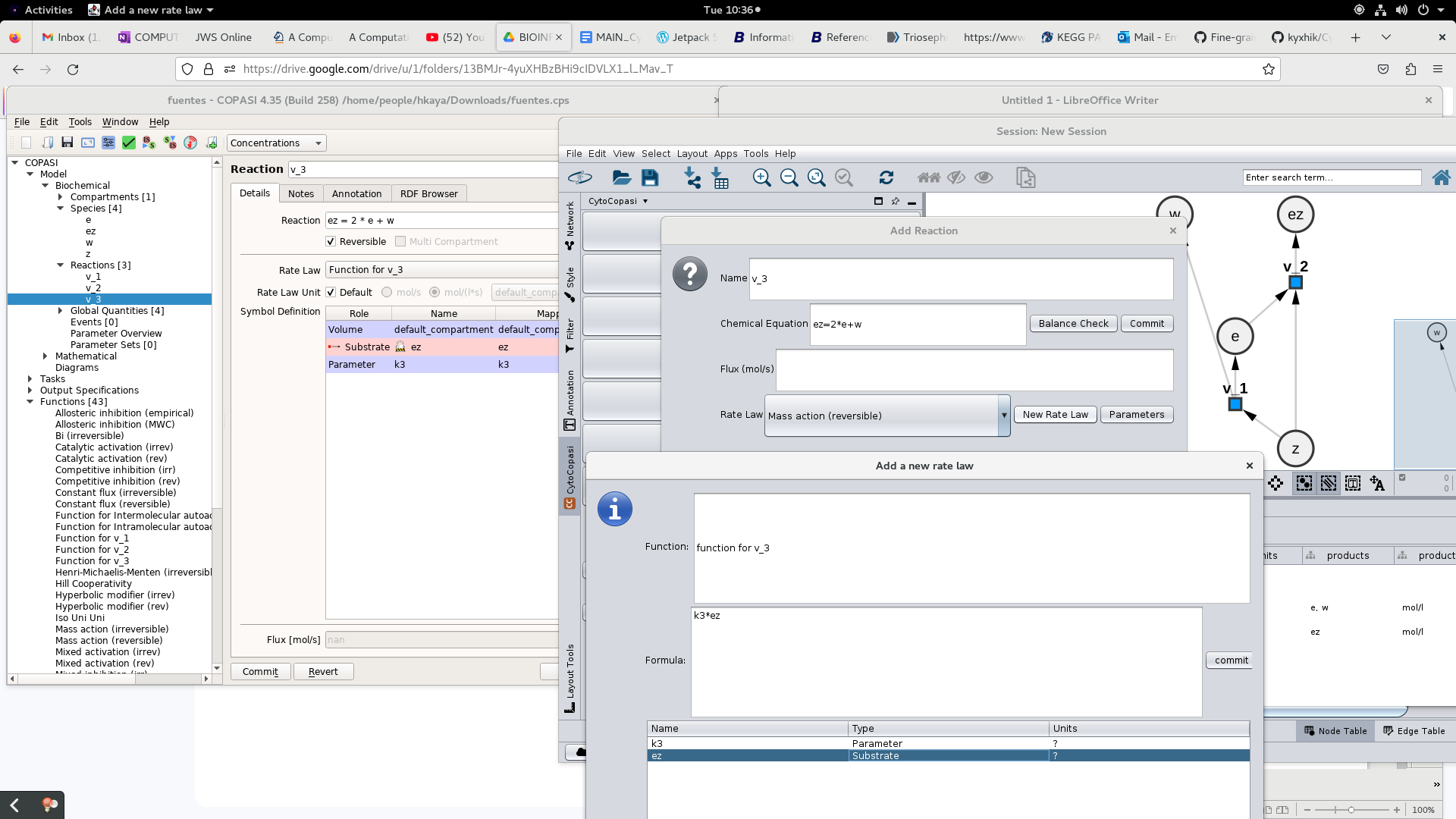
k22 = 0.00021 l/s

**Reaction: v\_3**

ez = 2\*e+w

Function for v\_3:

k3\*ez; k3 = 0.00054 l/s



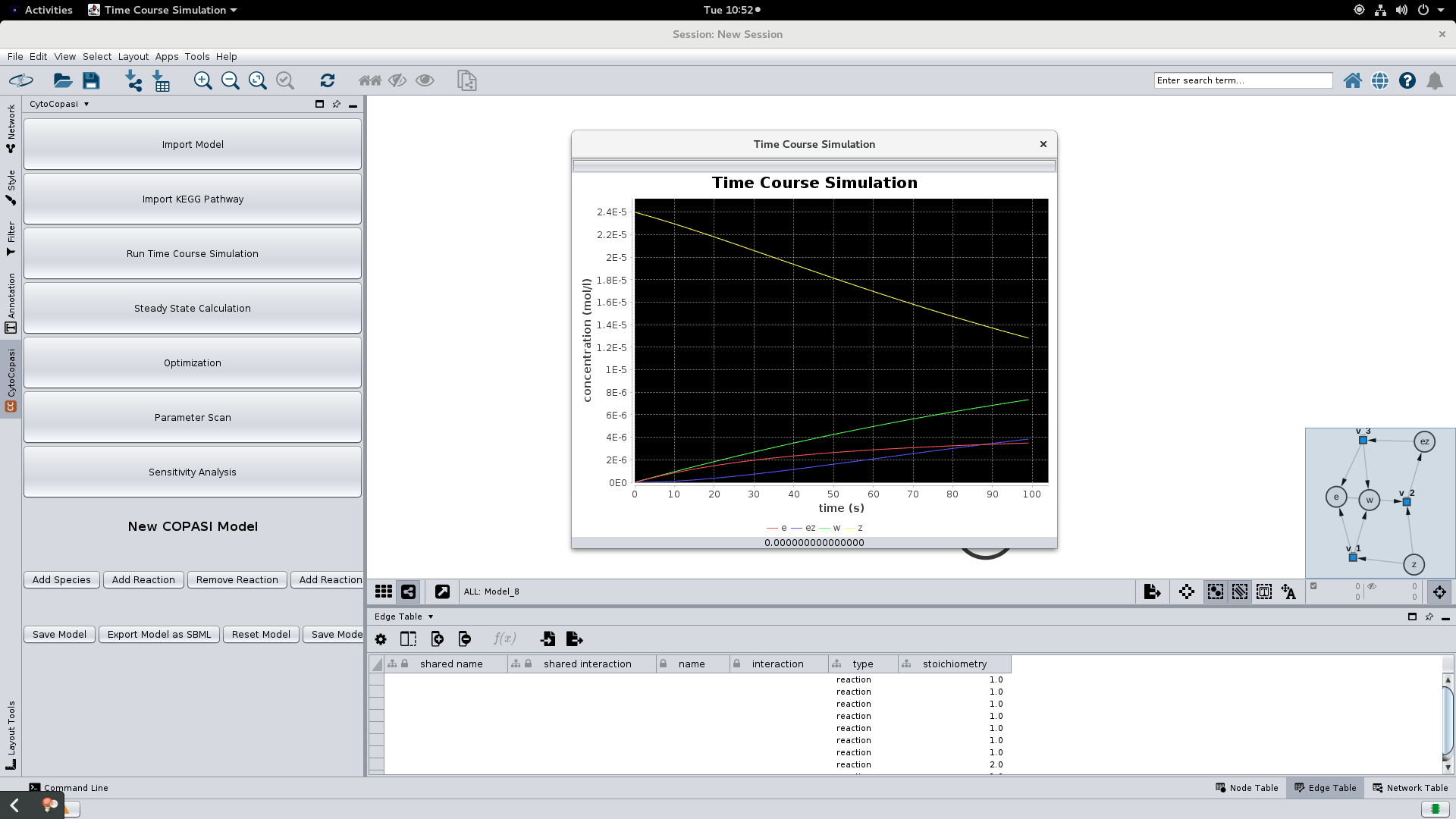
**Figure S2:** The reaction specifics for v\_3 entered into CytoCopasi and the resulting network view including all three reactions

When reactions are created, initial metabolite concentrations are set to 1.0 and status is set to “Reactions”. Double-click on the metabolite you want to edit.

[e]0, [ez]0, and [w]0 = 0.0 mol/l

[z]0 = 2.4 x 10-5 mol/l

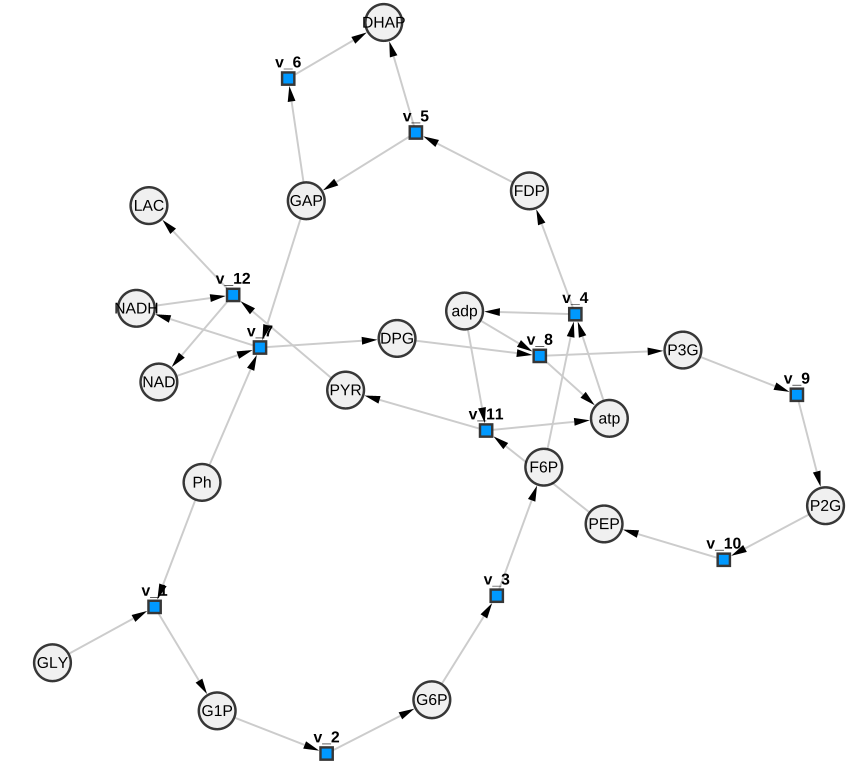
Now, run the time course with 100 seconds and 100 intervals to confirm that you constructed the model correctly.



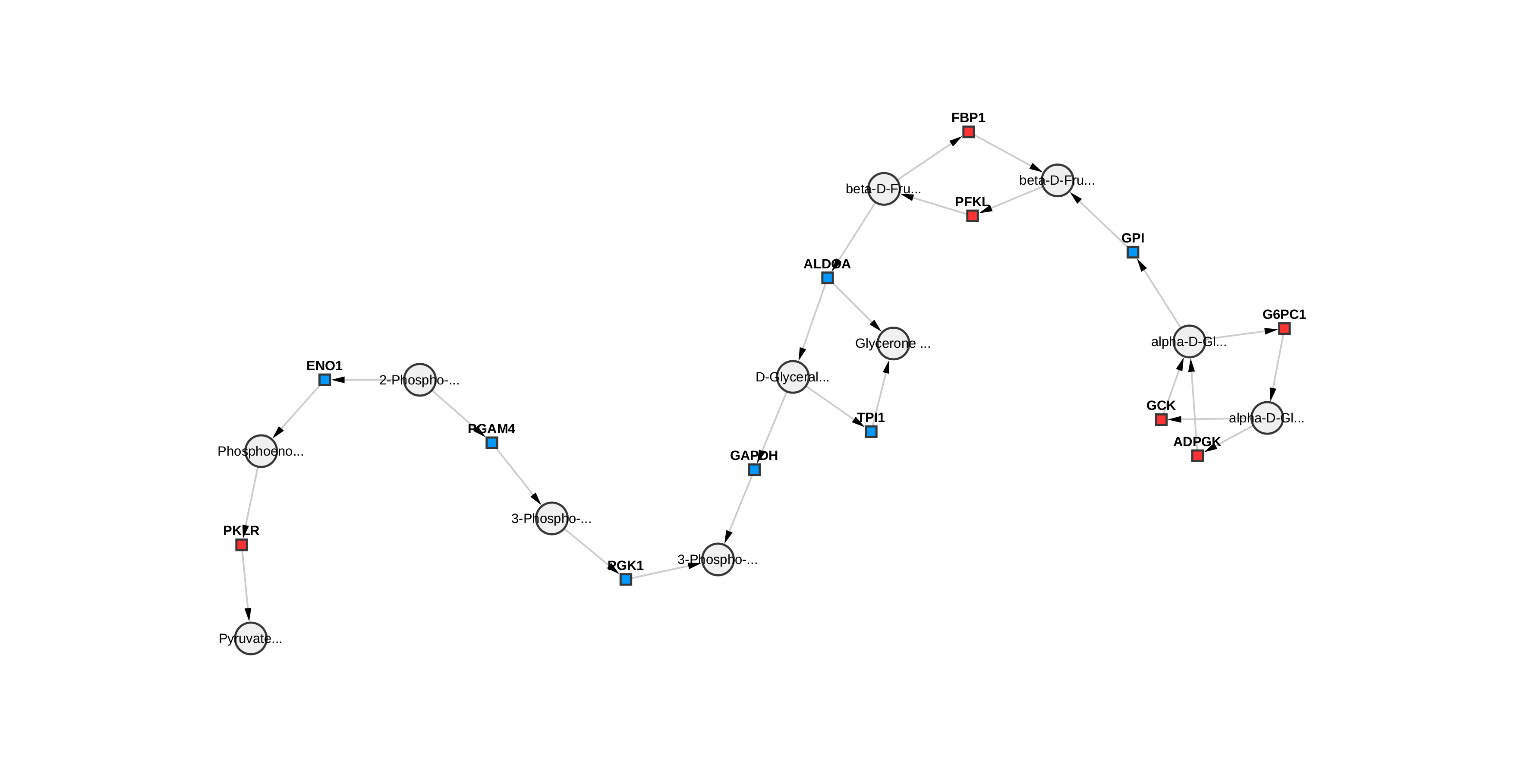
**Figure S3**: Running a time course simulation for 100 seconds to display the concentration profiles of the metabolites

## 2- Replicating Lambeth et al. [2] from the KEGG Glycolysis Model

The original SBML file



**Figure S4**: The Cytoscape network of the original model



**Figure S5**: The KEGG Glycolysis module M00002 (core module involving three-carbon compounds)

### 2.1 Metabolite Names

**Step 1: Rename the Metabolites**

Nomenclature:

GLY: glycogen

G1P: glucose 1-phosphate

G6P: glucose 6-phosphate

F6P: fructose 6-phosphate

FBP: fructose 1,6-bisphosphate

DHAP: glycerone phosphate (1,3-dihydroxyacetone phosphate)

GAP: D-glyceraldehyde 3-phosphate

DPG: 3-phospho-D-glyceryl phosphate

3PG: 3-phospho-D-glycerate

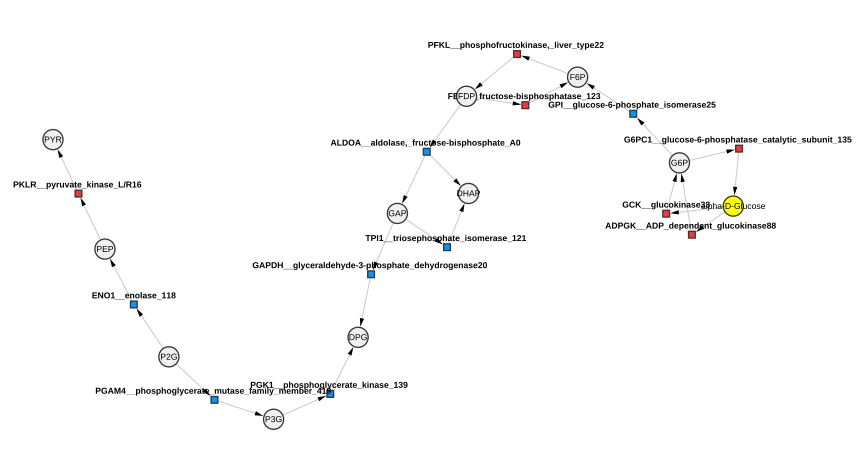
2PG: 2-phospho-D-glycerate

PEP: Phosphoenolpyruvate

PYR: Pyruvate

LAC: Lactate

Ph: inorganic phosphate



**Figure S6**: Metabolites have been renamed for ease of visualizing and customization

### 2.2 ADDING/REMOVING REACTIONS, CHANGING REACTION CHEMICAL EQUATIONS TO ADD NEW METABOLITES

Note: All the kinetics parameters are given in mM unless stated otherwise

**Step 2:** **Remove the reactions between G6P and alpha-D-Glucose** 

**Step 3: Add v\_2**

G1P = G6P

((Vfpglm\*G1P/Kpglmg1p)-(Vfpglm\*Kpglmg6p/(Kpglmg1p\*16.62))\*G6P/Kpglmg6p)/(1 + G1P/Kpglmg1p + G6P/Kpglmg6p)

Brenda Keyword: Phosphoglucomutase

EC to select: 5.4.2.2

It did not return parameters for Oryctolagus cuniculus (rabbit) nor Homo sapiens (human), therefore we pulled both parameters from the paper.

Kpglmg1p= 0.063 [3]

Kpglmg6p= 0.03 [3]

**Step 4: Add v\_1**

Ph + GLY = G1P

fracA\*((Vfgly\*Ph\*GLY/(KgpAigly\*KgpApi))/(1 + GLY/KgpAglyf + Ph/KgpApi + GLY\*Ph/(KgpAglyf\*KgpAipi) + GLY/KgpAglyb + G1P/KgpAg1p + GLY\*G1P/(KgpAig1p\*KgpAglyb)) - ((Vfgly\*KgpAglyb\*KgpAig1p/(KgpAigly\*KgpApi\*0.31))\*G1P\*GLY/(KgpAglyb\*KgpAig1p))/ (1 + GLY/KgpAglyf + Ph/KgpApi + GLY\*Ph/ (KgpAglyf\*KgpAipi) + GLY/KgpAglyb + G1P/KgpAg1p + GLY\*G1P/(KgpAig1p\*KgpAglyb))) + fracB\*((((amp^nH)/((Kgpamp^nH)\*0.02))/ (1 + (amp^nH)/((Kgpamp^nH)\*0.02))\*(Vfgly\*Ph\*GLY/(KgpBiglyf\*KgpBpi))/((1 + GLY/KgpBipi + Ph/KgpBiglyf + GLY/KgpBiglyb + G1P/KgpBig1p + GLY\*Ph/(KgpBiglyf\*KgpBpi) + GLY\*G1P/(KgpBg1p\*KgpBiglyb)))) - (((amp^nH)/((Kgpamp^nH)\*0.02))/(1 + (amp^nH)/((Kgpamp^nH)\*0.02))\*((Vfgly\*KgpBg1p\*KgpBiglyb/(KgpBiglyf\*KgpBpi\*0.31))\*G1P\*GLY/(KgpBg1p\*KgpBiglyb))/((1 + GLY/KgpBipi + Ph/KgpBiglyf + GLY/KgpBiglyb + G1P/KgpBig1p + GLY\*Ph/(KgpBiglyf\*KgpBpi) + GLY\*G1P/(KgpBg1p\*KgpBiglyb)))))

Keyword: Glycogen Phosphorylase

EC to select: 2.4.1.1

The Km values are pulled entirely from BRENDA, while the Ki values for Glycogen Phosphorylase B are from BRENDA, and those for Glycogen Phosphorylase A are from the paper.

Km:

KgpApi: 28 [4]

KgpAglyf: 0.62 [5]

KgpAglyb: 0.15 [5]

KgpAg1p: 1.7  [6]

Kgpamp: 0.074 [7]

KgpBpi: 11 [7]

KgpBg1p: 5.5 [7]

Ki: look at the commentary column to see what the inhibitor is being used against

KgpBipi= 0.71 [7]

KgpBig1p = 0.44 [7]

KgpBiglyf = 0.0028 [8]

KgpBiglyb = 5.9  [9]

We did not find inhibition constants for Glycogen Phosphorylase A, but the papers that contain Km constants can be checked by the user to see if they contain inhibition constants as well. For now, we are going to use the values from the original paper.

KgpAigly = 2 [10]

KgpAiPi = 4 [10]

KgpAig1p = 10.1 [10]

**Step 5: The reaction F6P=FDP is defined as one reversible reaction in the SBML model, whereas Kegg has a separate reaction node for the reverse reaction (because of different enzymes being involved). So:** **Delete FBP1 – fructose biphosphatase and Change the Chemical equation for PFKL\_phosphofructokinase**

F6P + atp = FDP + adp

(Vfpfk\*atp\*F6P\*(1 + (Kpfkatp\*Kpfkf6p\*Lo\*(1 + (en\*amp)/Kpfkamp)^4\*(1 + atp/Kpfkiatp)^4\*((1 + atp/KpfkatpT)\*(1 + F6P/Kpfkf6pT) + FDP/KpfkfdpT + (adp\*(1 + FDP/KpfkfdpT))/KpfkadpT)^3)/(KpfkatpT\*Kpfkf6pT\*(1 + amp/Kpfkamp)^4\*(1 + (dn\*atp)/Kpfkiatp)^4\*((1 + atp/Kpfkatp)\*(1 + F6P/Kpfkf6p) + FDP/Kpfkfdp + (adp\*(1 + FDP/Kpfkfdp))/Kpfkadp)^3)))/(Kpfkatp\*Kpfkf6p\*((1 + atp/Kpfkatp)\*(1 + F6P/Kpfkf6p) + FDP/Kpfkfdp + (adp\*(1 + FDP/Kpfkfdp))/Kpfkadp)\*(1 + (Lo\*(1 + (en\*amp)/Kpfkamp)^4\*(1 + atp/Kpfkiatp)^4\*((1 + atp/KpfkatpT)\*(1 + F6P/Kpfkf6pT) + FDP/KpfkfdpT + (adp\*(1 + FDP/KpfkfdpT))/KpfkadpT)^4)/((1 + amp/Kpfkamp)^4\*(1 + (dn\*atp)/Kpfkiatp)^4\*((1 + atp/Kpfkatp)\*(1 + F6P/Kpfkf6p) + FDP/Kpfkfdp + (adp\*(1 + FDP/Kpfkfdp))/Kpfkadp)^4))) - (0.004117429077284144\*Vfpfk\*adp\*FDP\*(1 + (Kpfkatp\*Kpfkf6p\*Lo\*(1 + (en\*amp)/Kpfkamp)^4\*(1 + atp/Kpfkiatp)^4\*((1 + atp/KpfkatpT)\*(1 + F6P/Kpfkf6pT) + FDP/KpfkfdpT + (adp\*(1 + FDP/KpfkfdpT))/KpfkadpT)^3)/(KpfkatpT\*Kpfkf6pT\*(1 + amp/Kpfkamp)^4\*(1 + (dn\*atp)/Kpfkiatp)^4\*((1 + atp/Kpfkatp)\*(1 + F6P/Kpfkf6p) + FDP/Kpfkfdp + (adp\*(1 + FDP/Kpfkfdp))/Kpfkadp)^3)))/(Kpfkatp\*Kpfkf6p\*((1 + atp/Kpfkatp)\*(1 + F6P/Kpfkf6p) + FDP/Kpfkfdp + (adp\*(1 + FDP/Kpfkfdp))/Kpfkadp)\*(1 + (Lo\*(1 + (en\*amp)/Kpfkamp)^4\*(1 + atp/Kpfkiatp)^4\* ((1 + atp/KpfkatpT)\*(1 + F6P/Kpfkf6pT) + FDP/KpfkfdpT + (adp\*(1 + FDP/KpfkfdpT))/KpfkadpT)^4)/((1 + amp/Kpfkamp)^4\*(1 + (dn\*atp)/Kpfkiatp)^4\*((1 + atp/Kpfkatp)\*(1 + F6P/Kpfkf6p) + FDP/Kpfkfdp + (adp\*(1 + FDP/Kpfkfdp))/Kpfkadp)^4)))

Keyword: Phosphofructokinase

EC to select: 2.7.1.11

It is best to pull the values from the original paper since all the values were obtained from rabbit.

Kpfkf6p: 0.18 [11]

Kpfkf6pT= 20 [11]

Kpfkatp= 0.08 [11]

KpfkatpT= 0.25 [11]

Kpfkiatp= 0.87 [11]

Kpfkfdp= 4.02 [12]

KpfkfdpT= 4.02 [12]

Kpfkadp= 2.7 [12]

KpfkadpT= 2.7 [12]

Kpfkamp = 0.06 [12]

**Step 6:** **Change Reaction GAP=DPG**

GAP + NAD + Ph = DPG + NADH

((-11.235955056179776\*Vfgad\*DPG\*NADH)/(Kgapdhgap\*Kgapdhnad\*Kgapdhpi) + (Vfgad\*GAP\*NAD\*Ph)/(Kgapdhgap\*Kgapdhnad\*Kgapdhpi))/(1 + DPG/Kgapdh13dpg + GAP/Kgapdhgap + NAD/Kgapdhnad + (GAP\*NAD)/(Kgapdhgap\*Kgapdhnad) + NADH/Kgapdhnadh + (DPG\*NADH)/(Kgapdh13dpg\*Kgapdhnadh) + Ph/Kgapdhpi + (GAP\*NAD\*Ph)/(Kgapdhgap\*Kgapdhnad\*Kgapdhpi))

Keyword: Glyceraldehyde-3-Phosphate Dehydrogenase

EC to select: 1.2.1.12

Rabbit: **80% complete with BRENDA, one value from the original paper**

Kgapdhnadh=0.012 [13]

Kgapdhnad = 0.06 [13]

Kgapdhgap = 0.82 [13]

Kgapdh13dpg = 0.13 [13]

From paper:

Kgapdhpi = 0.29 [14]

**Step 7:** **Change Reaction DPG=P3G**

DPG + adp = P3G + atp

((57109\*Vbpgk\*adp\*DPG)/(Kpgk3pg\*Kpgkatp) - (Vbpgk\*atp\*P3G)/(Kpgk3pg\*Kpgkatp))/(1 + adp/Kpgkadp + atp/Kpgkatp + DPG/Kpgk13dpg + (adp\*DPG)/(Kpgk13dpg\*Kpgkadp) + P3G/Kpgk3pg + (atp\*P3G)/(Kpgk3pg\*Kpgkatp))

Keyword: Phosphoglycerate Kinase

EC to select: 2.7.2.3

All the values are pulled from BRENDA (for Homo sapiens)

Kpgk3pg = 0.1 [15]

Kpgkatp = 0.11 [15]

Kpgkadp = 0.1 [15]

Kpgk13dpg = 0.0077 [15]

**Step 8:** **Change PEP->PYR**

PEP + adp = PYR + atp

(Vfpk\*PEP\*adp/(Kpkpep\*Kpkadp)-(Vfpk\*Kpkpyr\*Kpkatp/(Kpkpep\*Kpkadp\*10304))\*PYR\*atp/(Kpkpyr\*Kpkatp))/(1+PEP/Kpkpep+adp/Kpkadp + PEP\*adp/(Kpkpep\*Kpkadp) + atp/Kpkatp + PYR/Kpkpyr + PYR\*atp/(Kpkpyr\*Kpkatp))

Keyword: Pyruvate Kinase, organism: Oryctolagus cuniculus

EC no to select: 2.7.1.40

The Km values for PEP and ADP are pulled from BRENDA, and those for PYR and ATP are from the original paper.

Kpkpep = 0.076 [16]

Kpkadp = 0.357 [16]

Kpkpyr = 7.05 [17]

Kpkatp = 1.13 [17]

**Step 9:** **Add the Reaction for Lactate**

PYR + NADH = LAC + NAD

((Vfldh\*PYR\*NADH/(Kldhpyr\*Kldhnadh))-((Vfldh\*Kldhlac\*Kldhnad/(Kldhpyr\*Kldhnadh\*16198))\*LAC\*NAD/(Kldhlac\*Kldhnad)))/(1 + PYR/Kldhpyr + NADH/Kldhnadh + PYR\*NADH/(Kldhpyr\*Kldhnadh) + LAC/Kldhlac + NAD/Kldhnad + LAC\*NAD/(Kldhlac\*Kldhnad))

Keyword: Lactate dehydrogenase; Organism: Homo sapiens

EC no: 1.1.1.28

3 out of 4 parameters were available on BRENDA:

Kldhpyr= 0.398 [18]

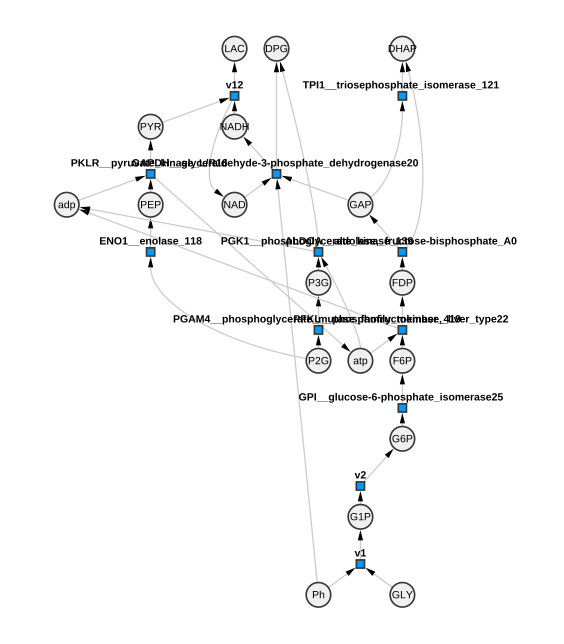
Kldhnad = 0.5 [19]

Kldhlac = 10.73 [19]

From the original paper:

Kldhnadh = 0.002 [20]

**Final view (with Hierarchical Layout instead of force-directed)**



**Figure S7**: Final view (with Hierarchical Layout instead of force-directed)

### 2.3 MODIFYING RATE LAWS FOR THE OTHER REACTIONS (WHOSE EQUATIONS DID NOT NEED TO BE CHANGED, BUT HAD CUSTOM RATE LAWS)

**Step 10:** G6P = F6P

(((Vbpgi\*Kpgig6p/Kpgif6p\*0.45)\*G6P/Kpgig6p)-(Vbpgi\*F6P/Kpgif6p))/(1+F6P/Kpgif6p + G6P/Kpgig6p)

Keyword: Phosphoglucoisomerase; Organism: Oryctolagus cuniculus

EC no: 5.3.1.9

Both Km values are available on BRENDA

Kpgif6p = 0.01 [21]

Kpgig6p = 0.03 [21]

**Step 11:** FDP = DHAP + GAP

((Vfald\*FDP/Kaldfdp)- ((Vfald\*Kaldgap\*Kalddhap/(Kaldfdp\*0.000095))\*DHAP\*GAP/(Kaldgap\*Kalddhap)))/(1+FDP/Kaldfdp+GAP/Kaldgap + DHAP/Kalddhap)

Keyword: Aldolase; Organism: Oryctolagus cuniculus

EC=4.1.2.13

All three Km values are available on BRENDA.

Kaldfdp = 0.06 [22]

Kaldgap = 1 [22]

Kalddhap = 2 [22]

**Step 12:** GAP = DHAP

((Vftpi\*GAP/Ktpigap)-((Vftpi\*Ktpidhap/(Ktpigap\*19.2))\*DHAP/Ktpidhap))/(1 + GAP/Ktpigap + DHAP/Ktpidhap)

Keyword: triose-phosphate isomerase; Organism: Oryctolagus cuniculus

E.C. 5.3.1.1

Both Km ­values are available on BRENDA

Ktpigap = 0.42 [23]

Ktpidhap = 0.75 [23]

**Step 13:** P3G = P2G

((Vfpgm\*P3G/Kpgm3pg)-((Vfpgm\*Kpgm2pg/(Kpgm3pg\*0.18))\*P2G/Kpgm2pg))/(1+P3G/Kpgm3pg + P2G/Kpgm2pg)

Keyword: Phosphoglycerate Mutase; Organism: Homo sapiens

EC: 5.4.2.11

From BRENDA

Kpgm3pg = 0.4 [24]

No value of Kpm2pg for homo sapiens on BRENDA. That said, there are very few results available with P2G as the substrate.

From paper: 0.014 (chicken) [25]

**Step 14:** P2G = PEP

((Vfen\*P2G/Ken2pg)-((Vfen\*Kenpep/(Ken2pg\*0.49))\*PEP/Kenpep))/(1+P2G/Ken2pg + PEP/Kenpep)

Keyword: Enolase; Organism: Oryctolagus cuniculus

EC no: 4.2.1.11

Ken2pg = 0.061 [26]

Kenpep = 0.25 [26]

## 3- Reactions for Drug Treatment with Vemurafenib or Dabrafenib

### 3.1 Treatment with Vemurafenib

The following reaction was added to ERK\_Akt\_Wnt\_SBML-BRaf.cps to construct the Vemurafenib treated version ERK\_Akt\_Wnt\_SBML-BRaf-Vem.cps

Rate Law: Modified Michaelis-Menten

Kcat = 1/s

Km = 100 nM

[Vem]\_0 = 1000 nM

### 3.2 Treatment with Dabrafenib

The following reactions were added to ERK\_Akt\_Wnt\_SBML-BRaf.cps to construct the Dabrafenib treated version ERK\_Akt\_Wnt\_SBML-BRaf-DFB.cps

Note: Mass action (reversible) is selected as the rate law for all the reactions below.

|  |  |  |
| --- | --- | --- |
| Constant | Value | Reference |
| a2 | 0.106 µM-1s-1 | [27] |
| d2 | 0.02385 s-1 | [28] |
| a4 | 0.106 µM-1s-1 | [27] |
| d4 | 0.0000593 s-1 | [28] |

**Table S1**: Kinetic Constants used for Dabrafenib-related reactions

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