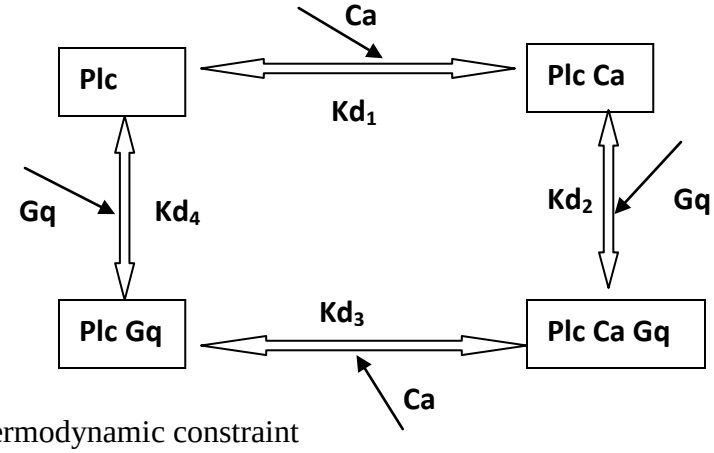
Combined Documentation

Three simulations were carried out named Kimetal2013, oldMSPN and newMSPN. In all simulations, when changing the Ca threshold, we kept in mind the thermodynamic constraints.



So, as per thermodynamic constraint

$Kd_1 * Kd_2 = Kd_4 * Kd_3$

In both the simulations both Kd_1 and Kd_3 were scaled with same values.

First we summarize the simulation result for the Kimetal2013 model but using a lower Ca threshold for PLC.

The critical enzymes for 2AG production are phospholipase C (PLC) and diacylglycerol (DAG) lipase, both of which function as coincidence detectors. PLC produces DAG when activated by calcium binding, but the activity of the calcium bound PLC is markedly increased by GaqGTP binding. The DAG produced by PLC is converted to 2AG by DAG lipase, but the rate of this conversion is enhanced by calcium elevation. Accordingly in the model, DAG is produced from PLC even in the absence of Gq coupled (mGluR) receptor activation, but the quantity of DAG is enhanced by the GaqGTP produced by mGluR activation. The increased DAG production is translated into increased 2AG.

The three simulations that were carried out are as follows:

1. **Kimetal Original MSPN Table**: Simulations were carried out keeping all the reaction rates same as the Kim et al paper, Keeping thermodynamic constraints in mind following changes were made.

In Plc+Ca ->PlcCa reaction. original Kd = 6 μM new Kd= 1.5 μM
PlcGq+Ca -> PlcGqCa original Kd = 0.5 μM new Kd = 0.125 μM

to reduce Kd, in Plc+Ca ->PlcCa reaction
Kb was changed from 120 to 30 so Kd = kb/Kf = 30/0.02 = 1500 nM = 1.5 μM

And in PlcGq+Ca -> PlcGqCa

Kb was changed from 40 to 10 so Kd = kb/Kf = 10/0.08 = 125 nM =0.125µM

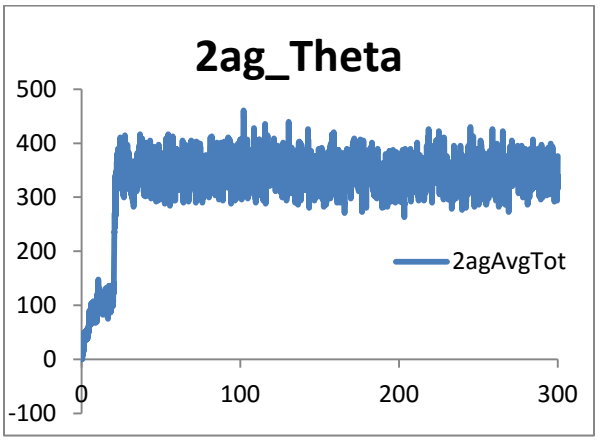
The simulations are as follows:

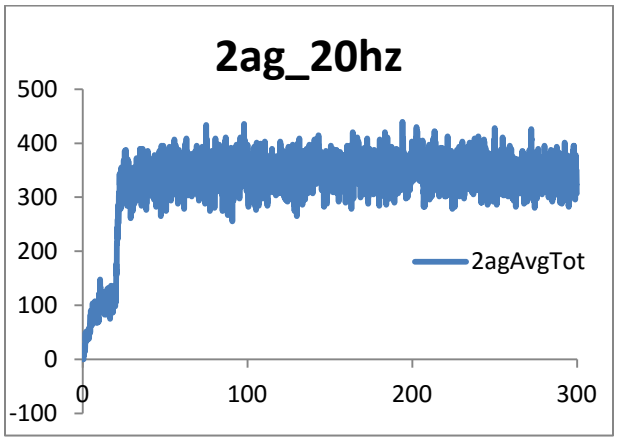
a. Theta burst simulations with updated PLC reaction rates (Theta_Kimetal)

b. 20Hz simulations with updated PLC reaction rates (20hz_Kimetal)

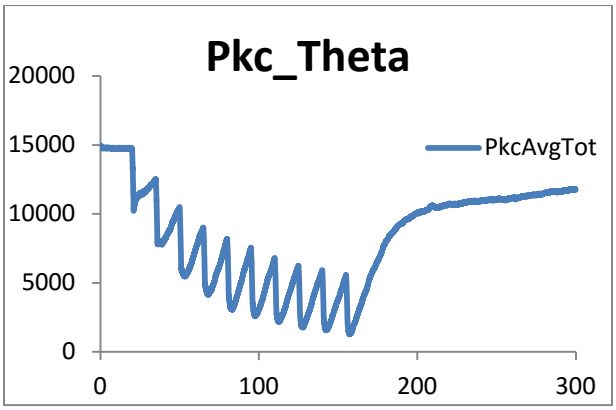
Plots

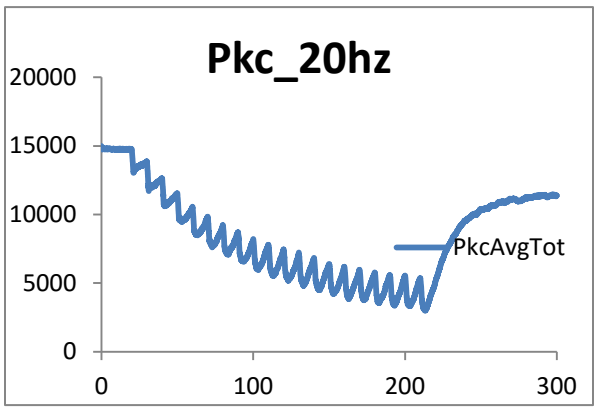
2ag



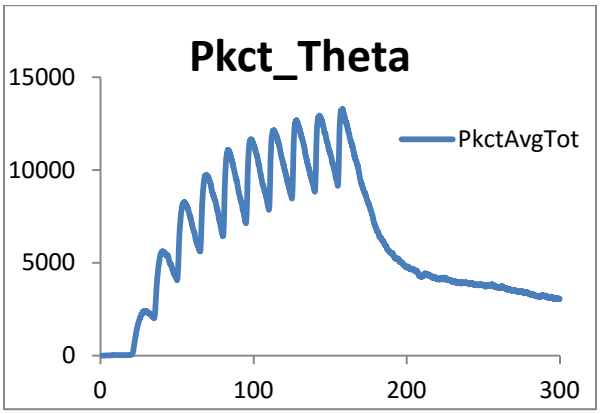


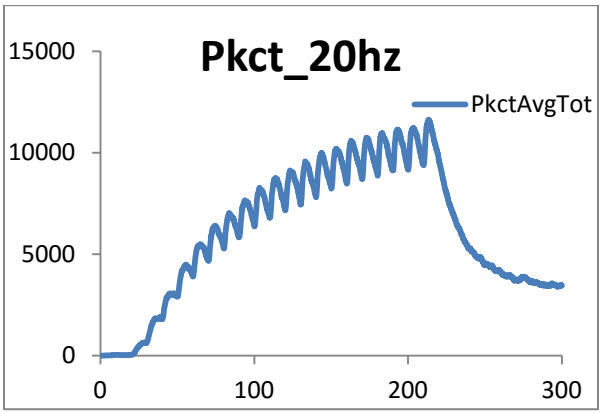
Pkc



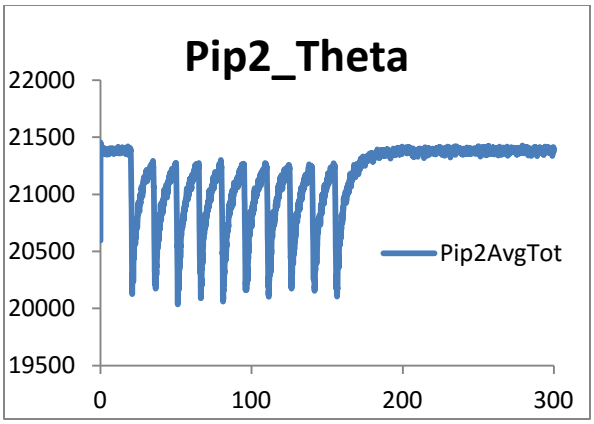


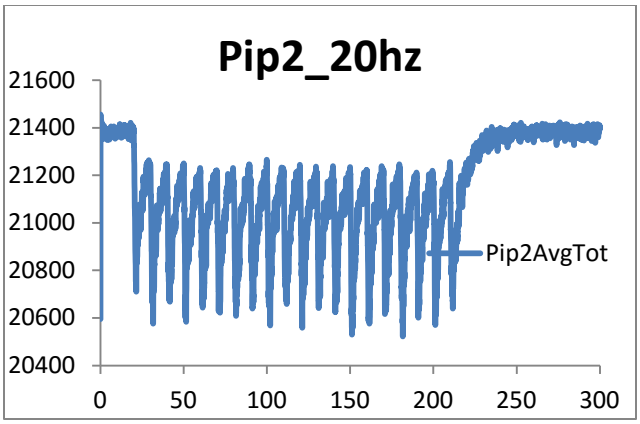
- Pkct



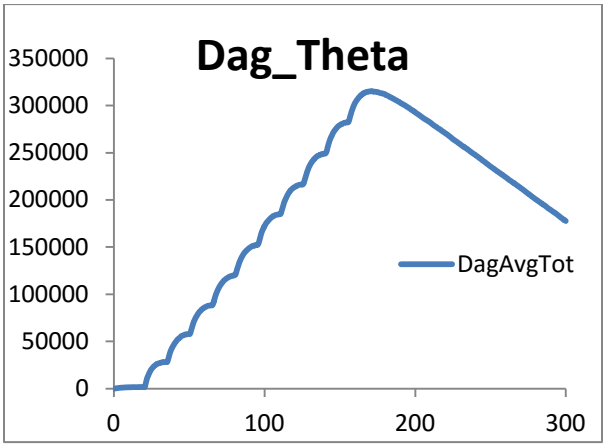


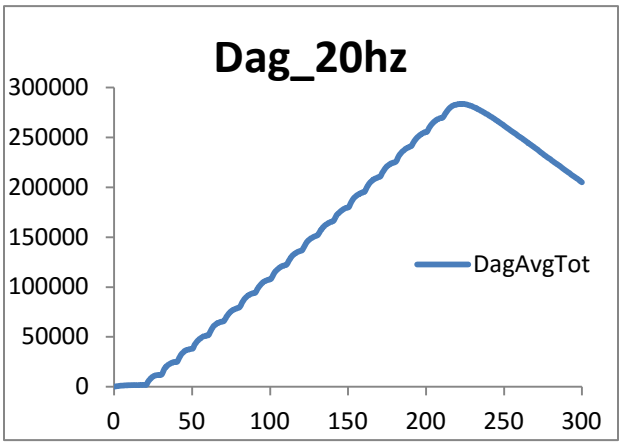
- Pip2



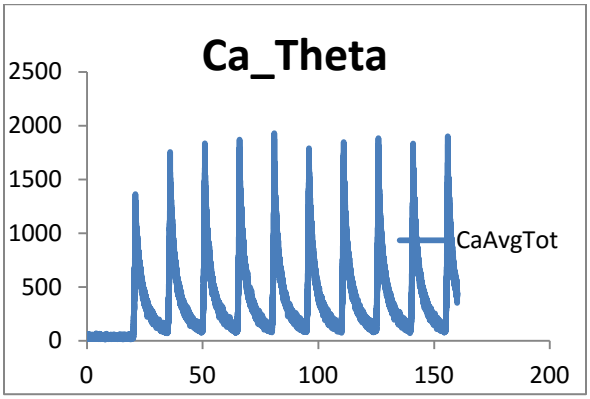


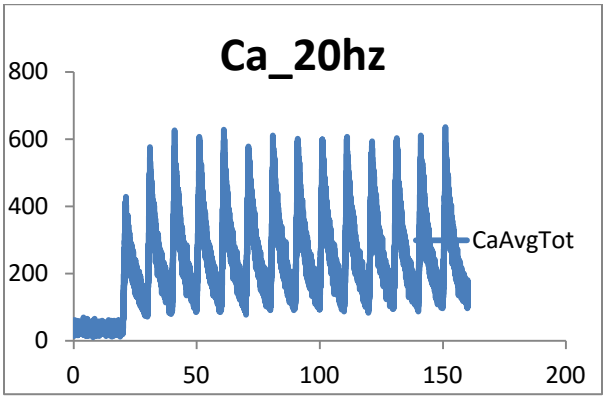
- Dag





- Ca





Also the lowered thresholds for Ca binding to PLC could affect the basal ca levels, thus we investigated that but it seems the Ca pumps, buffers, etc are taking care of the Ca levels in a robust way.

The conclusions from above was that the original Kim et al model was robust, however, the qualitative behavior for 20Hz vs theta stimulation might depend on the Ca threshold a bit.

2**. Old MSPN table (November 2015):** The updated PLC values were taken from the old MSPN table put up in github inNovember 2015. The following simulations were carried out:

a) Theta burst simulations with updated PLC values and PLC initial values doubled (Theta_oldMSPN)
b) 20Hz simulations with updated PLC values and PLC initial values doubled (20hz_oldMSPN)

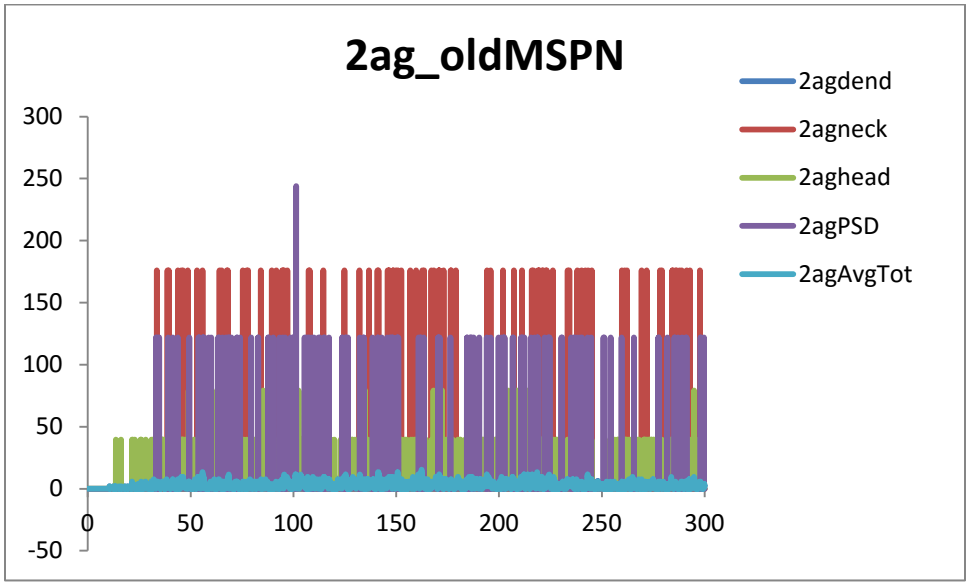
Now we summarize the observations made using the old MSPN model:

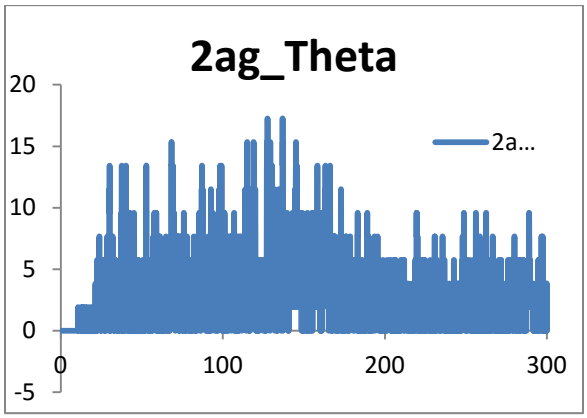
Reaction Equation	**kf (nM^{-1} s^{-1})**	**kb (s^{-1})**	**kcat (s^{-1})**	**Kd or Km (nM)**
Plc + Ca ⇔ PlcCa	0.0005	0.75		1500.00
PlcCa + GqaGTP ⇔ PlcCa-GqaGTP → PlcCa+GaqGDP	0.0035	0.7	30	200.00
PlcCa + PIP2 ⇔ PlcCaPIP2 ⇒ PlcCaDag + Ip3	1.00E-005	0.36	0.09	45000.00
Plc + GqaGTP ⇔ PlcGqaGTP → PLC+GaqGDP	0.0007	0.7	30	1000.00
PlcGqaGTP + Ca ⇔ PlcCaGqaGTP	0.0025	0.75		300.00
PlcCaGqaGTP + PIP2 ⇔ PlcCaGqaGTPPIP2 ⇒ PlcCaGqaGTPDag + Ip3	0.0003333	12	3	45004.50

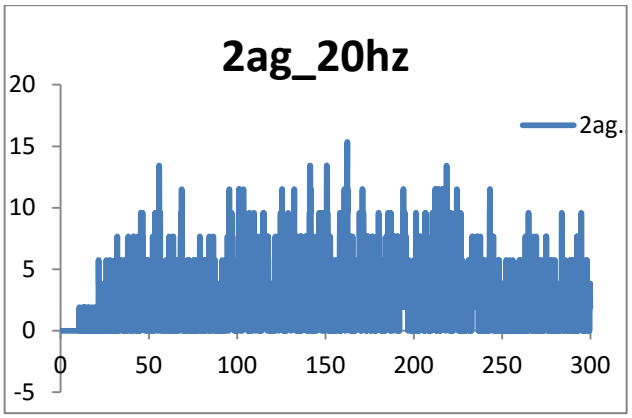
These updated values were taken from the old MSPN table and the reaction rates that were modified are in red. Also here we wanted to test a lower Ca threshold as the original value of 6 microM seemed to high.

The general conclusions were that the reactions seemed too slow.

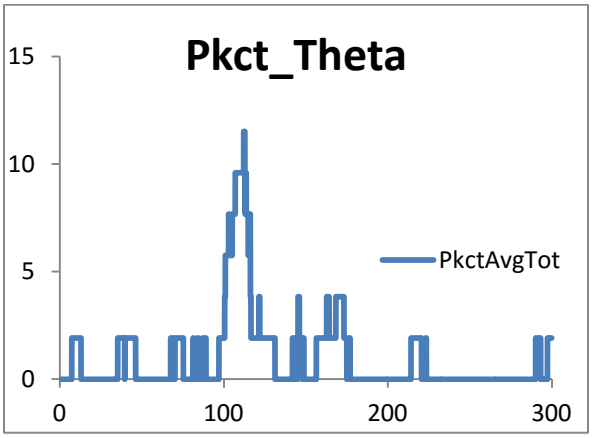
2ag




2ag_Theta
2a...
20
15
10
5
0
-5
0
100
200
300


2ag_20hz
2ag...
20
15
10
5
0
-5
0
50
100
150
200
250
300

Pkct


Pkct_Theta
PkctAvgTot
15
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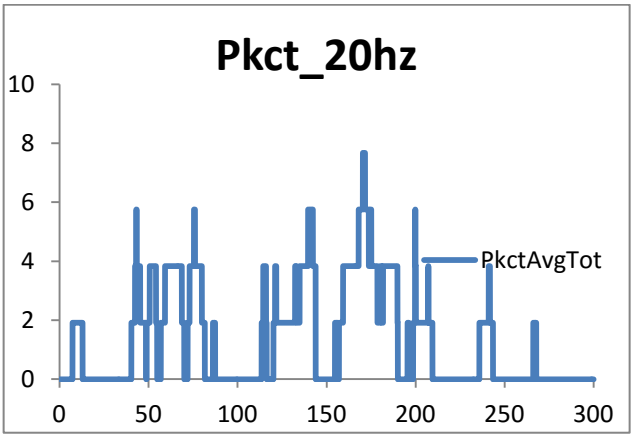
Pkct_20hz
PkctAvgTot
10
8
6
4
2
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50
100
150
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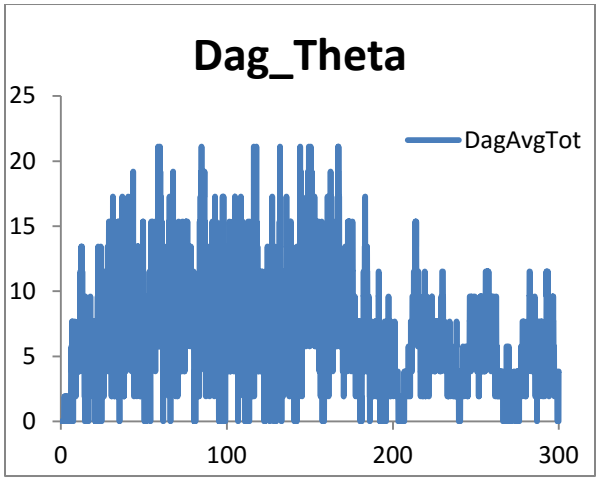
- Dag


Dag_Theta
DagAvgTot
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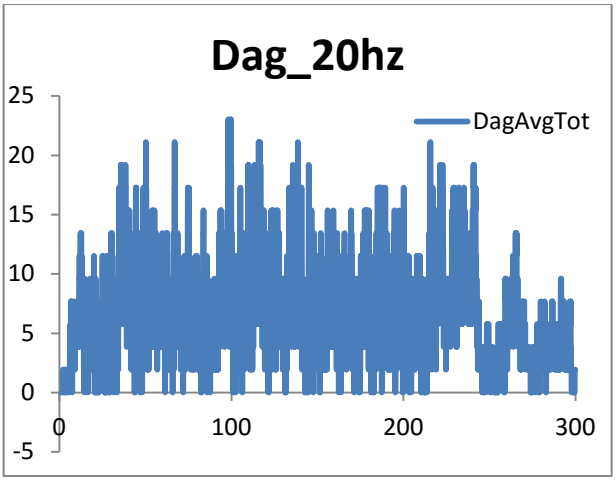
Dag_20hz
DagAvgTot
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20
15
10
5
0
-5
0
100
200
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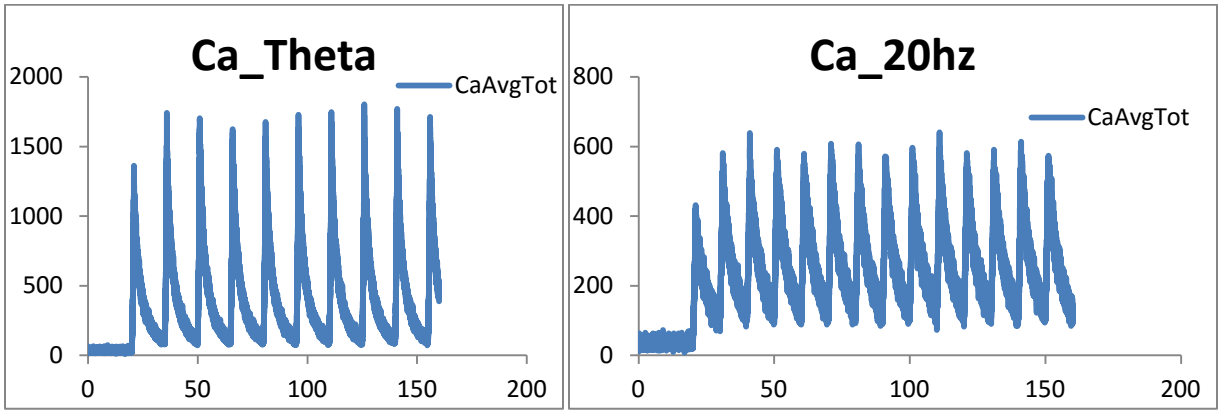
- Ca



3. New MSPN table 8th Jan 2016: Finally we now rerun the same simulations for the newer MSPN model 8th Jan 2016 parameters.

Still the rates of reaction are too slow for both the Theta and 20Hz. The activity of the calcium bound PLC is markedly increased by GaqGTP binding. Additionally with the slower reaction rate of PLCCaGqaGTP there is not much Pip2 which is being utilized for the production of DAG thus a slump in the production of DAG.

As there is less DAG produced so there is a little 2AG production in both the theta and 20Hz.

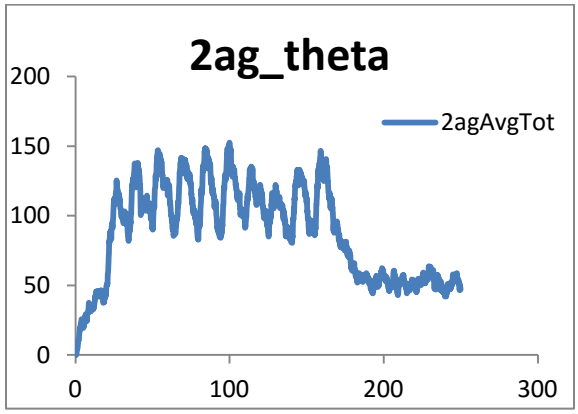
Also the PLC initial conditions were doubled.
In this case both the PlcCa and PlcCaGq complexes concentration increases. Because of an increase in both these complexes concentration the production of Dag increases manifold. Thus a significant increase in the production of 2ag.

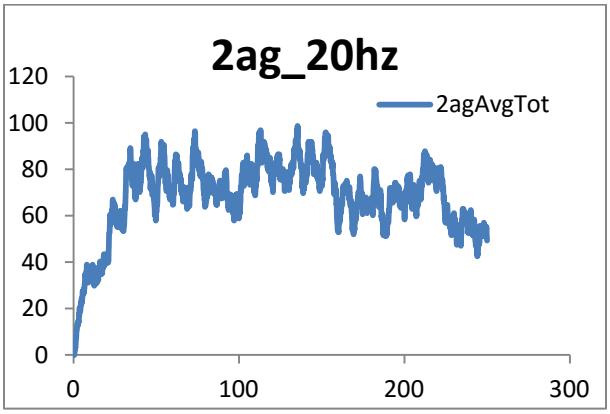
2. Two simulations were carried out keeping all the reaction rates as per the new MSPN table
    a) Theta burst simulations (Theta_NewMSPN)
    b) 20Hz simulations (20hz_NewMSPN)

These simulations were carried out with new NeuroRD 3 version. The DHPG is replaced by Glu. The 2ag produced is very low in both theta and 20hz as compared to the original plots of Kimetal paper.
In this case the reactions are too slow. One of the ways to speed up is to increase both Glu and Calcium.

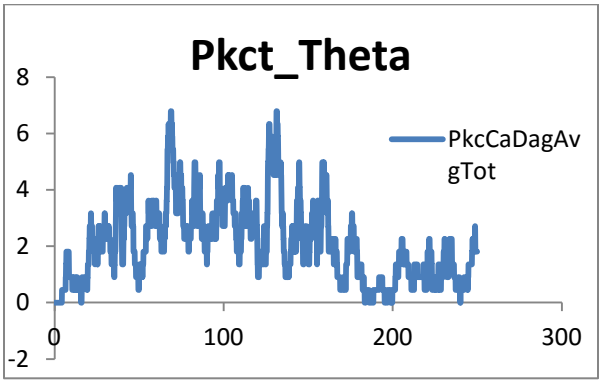
Plots

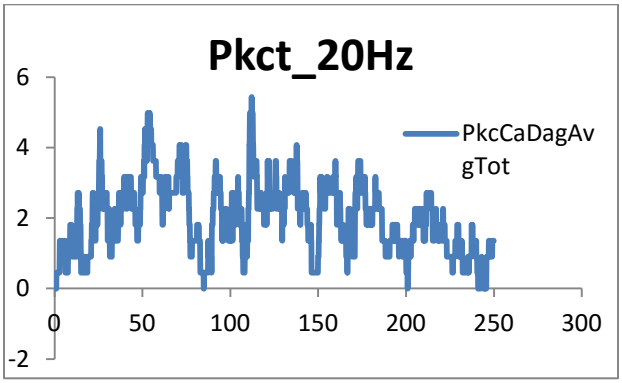
2ag



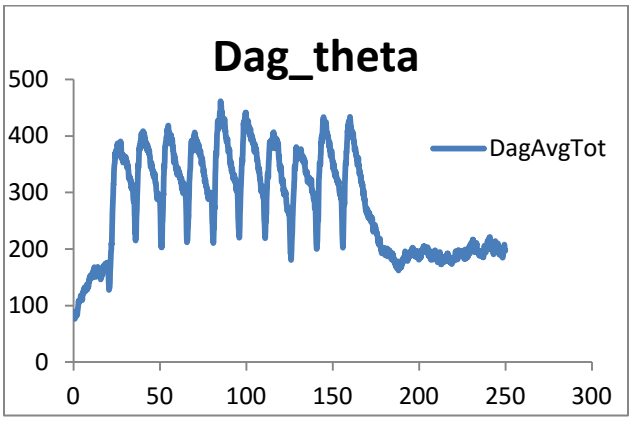


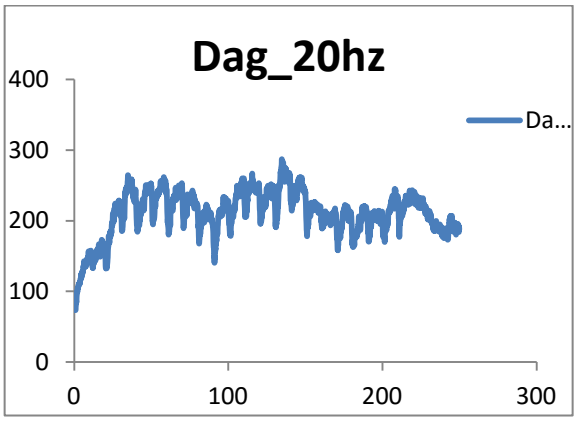
Pkct



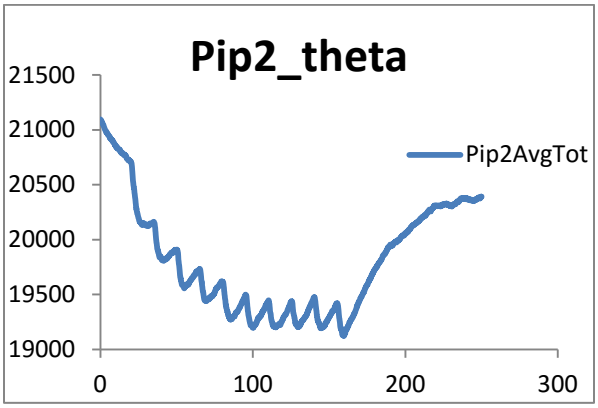


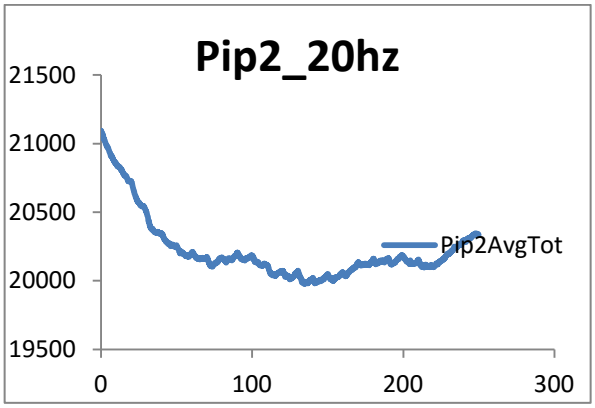
Dag



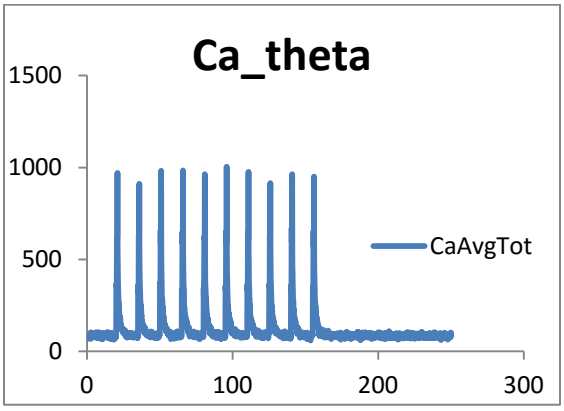


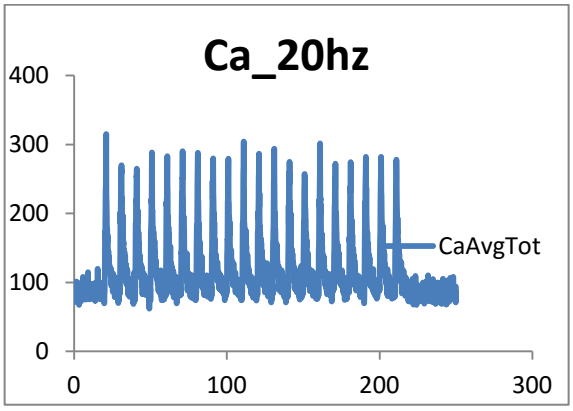
Pip2





Ca





Action points for the future:

- To update the new MSPN model based on the new parameters by Hille's lab (FRET data).
- Also explore better what happens if glutamate or the Ca signals increased.
- To counteract the pip2 deletion by Pip2 regeneration.