A Rule-based Model for LAT Phosphorylation and Aggregation

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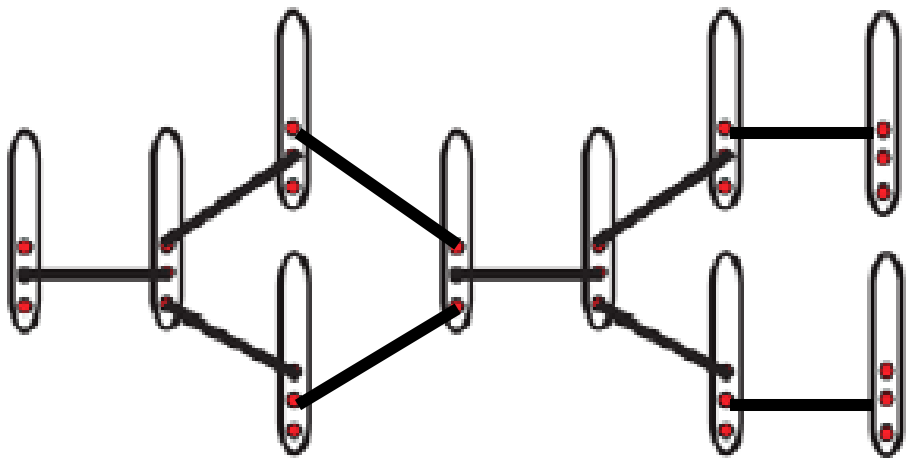
Cell Signaling Track (Q-bio 2)
6th Q-bio Summer School
Santa Fe campus

Introduction

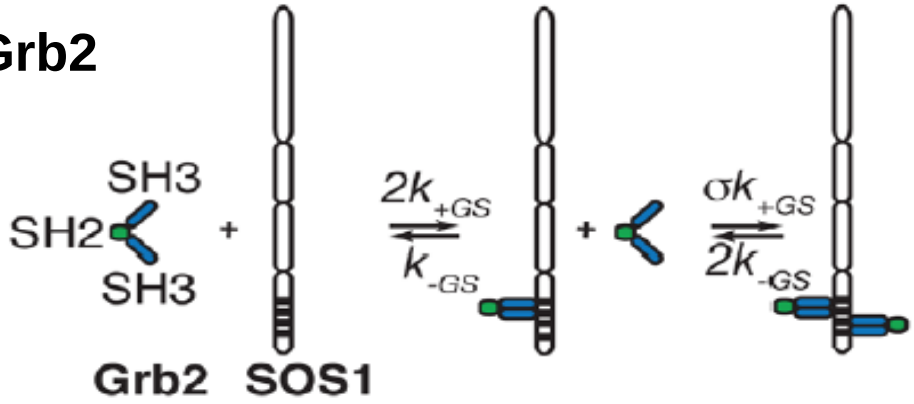
Biological Scenario: LAT aggregation



- LAT: the linker protein for activation of T cells
- Our Approach
  - To use a rule-based approach to represent the aggregation process of the LAT molecules

Interactions of LAT with Grb2 and SOS1

Grb2-SOS1-Grb2 Complex



Nag A et al. (2012) PLoS ONE 7: e28758
Houtman et al. (2006) Nature Structural & Molecular Biology 13(9)

Interactions of LAT with Grb2 and SOS1

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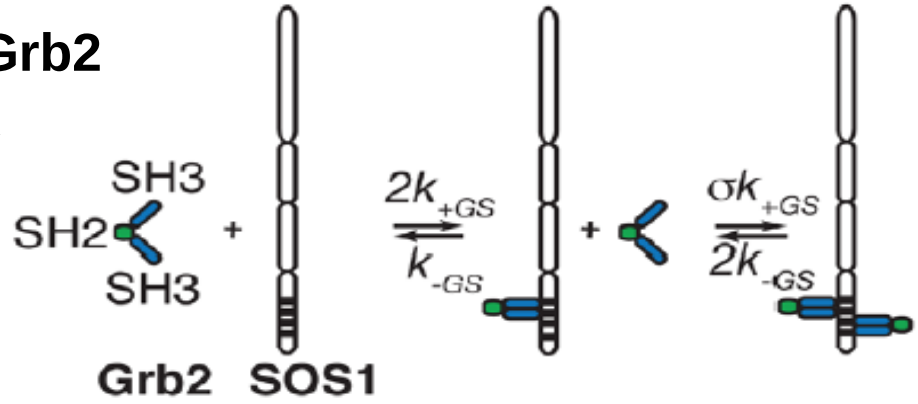
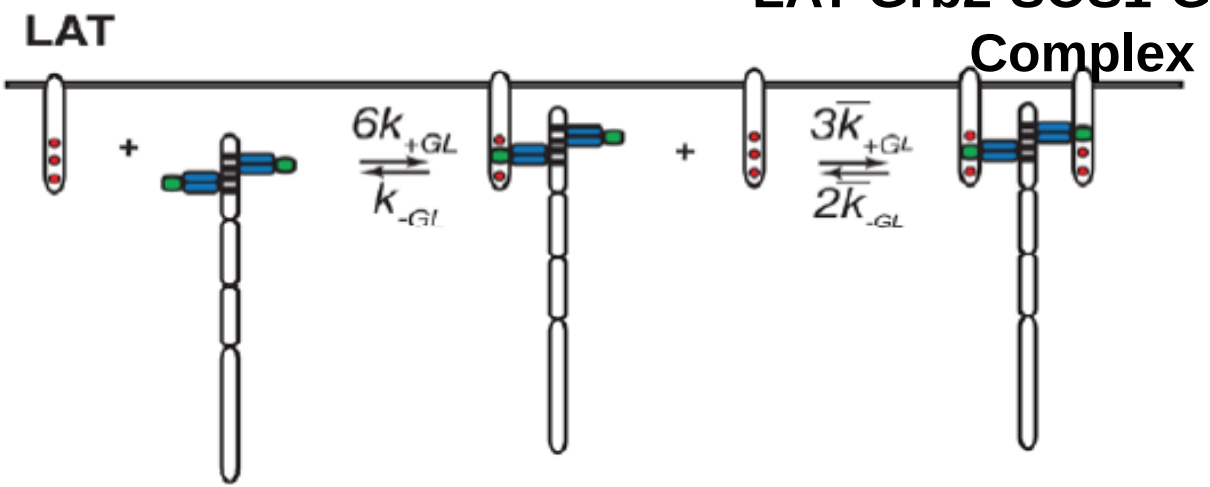


LAT-Grb2-SOS1-Grb2-LAT Complex



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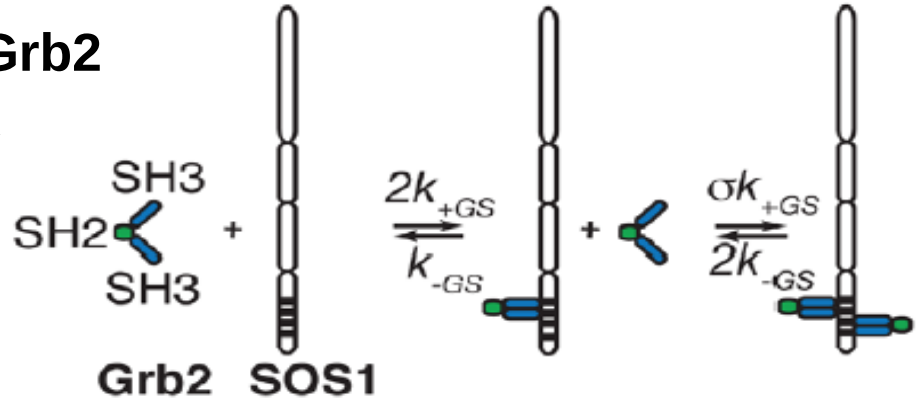
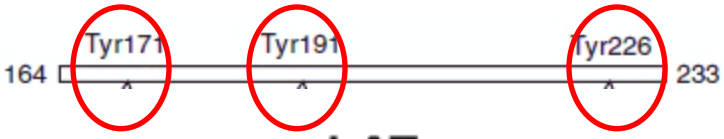
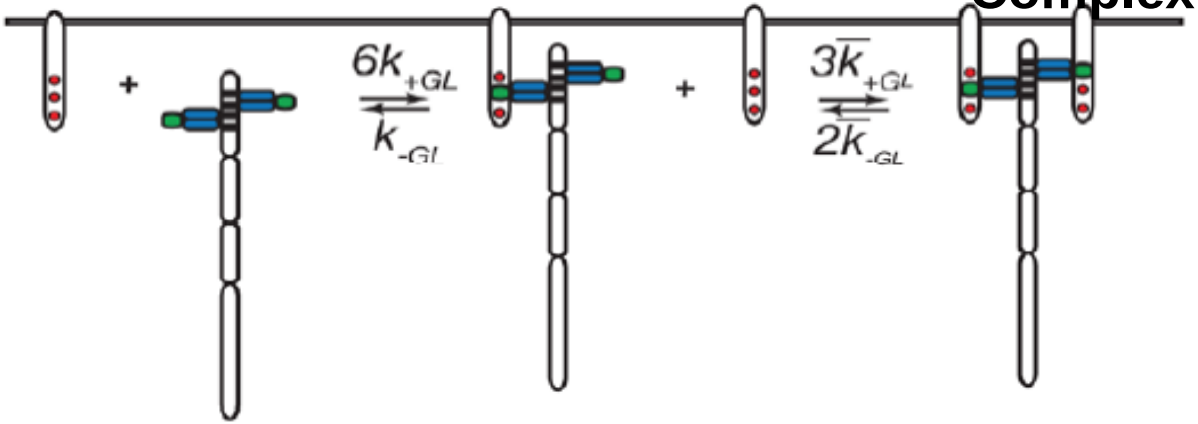




LAT-Grb2-SOS1-Grb2-LAT Complex



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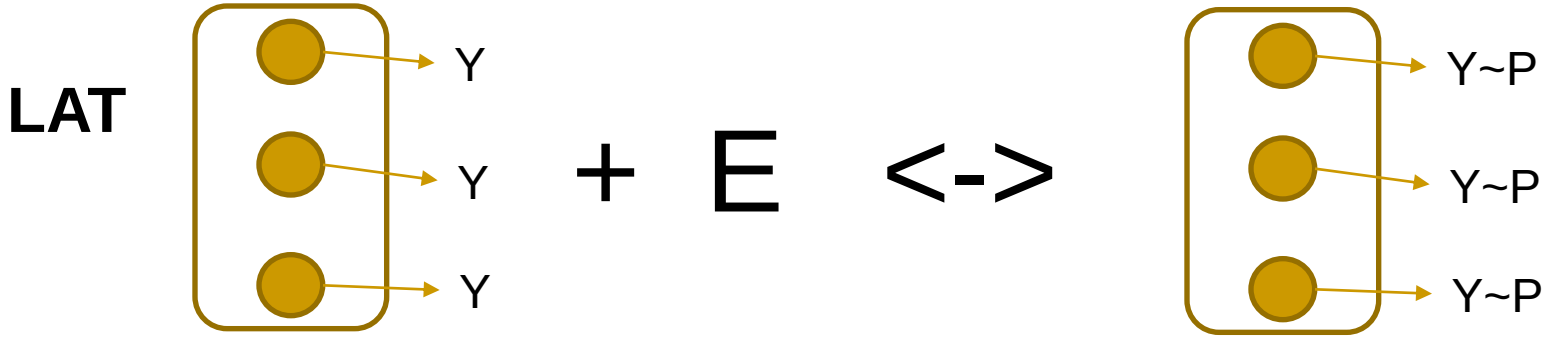
Rule-based Model for LAT

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begin reaction rules
#PHOSPHORYLATION RULES
#Encounter Complex
LAT(E~0,A~0) <-> LAT(E~1,A~0) Ekp,Ekm
LAT(E~1,A~1) -> LAT(E~0,A~0)  Ekm

#Binding Reactions
LAT(E~1,A~0,Y~U) <-> LAT(E~1!1,A~0,Y~U!1) Ekf1,Ekb
LAT(E~1,A~0,Y~P,Y~U,Y~U) <-> LAT(E~1!1,A~0,Y~P!1,Y~U,Y~U) Ekf2,Ekb
LAT(E~1,A~0,Y~P,Y~P,Y~U) <-> LAT(E~1!1,A~0,Y~P,Y~P!1,Y~U) Ekf3,Ekb
LAT(E~1,A~0,Y~P,Y~P,Y~P) <-> LAT(E~1!1,A~0,Y~P,Y~P,Y~P!1) Ekf4,Ekb

#Catalysis + Enzyme Inactivation
LAT(E~1!1,A~0,Y~U!1) -> LAT(E~1,A~1,Y~P,Y~U,Y~U) Ekc
LAT(E~1!1,A~0,Y~P!1,Y~U,Y~U) -> LAT(E~1,A~1,Y~P,Y~P,Y~U) Ekc
LAT(E~1!1,A~0,Y~P,Y~P!1,Y~U) -> LAT(E~1,A~1,Y~P,Y~P,Y~P) Ekc

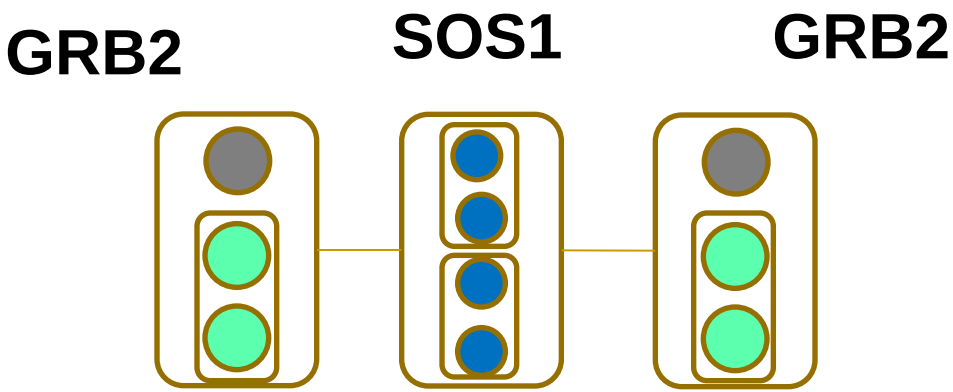
#Refactory Period
LAT(E~1,A~1) -> LAT(E~1,A~0) Emu
```

Phosphorylation of LAT sites

Heterogeneous LAT mixture: monovalent, bivalent, and trivalent

Dushek O et al. (2011) Biophys J 100, 1189-1197.

Rule-based Model for LAT



Binding of GRB2 and SOS1

```
# LAT AGGREGRATION RULES
# 1a: Free GRB2 binds free SOS1
GRB2(SH2,SH3) + SOS1(PRS,PRS) <-> GRB2(SH2,SH3!1).SOS1(PRS!1,PRS)   kgsp, kgsm

# 1b: Free GRB2 binds SOS1 bound to GRB2
GRB2(SH2,SH3) + SOS1(PRS,PRS!1).GRB2(SH2,SH3!1) <-> GRB2(SH2,SH3!2).SOS1(PRS!2,PRS!1).GRB2(SH2,SH3!1)   kxgsp, kxgsm

# 1c: Membrane-associated GRB2 binds free SOS1
GRB2(SH3,SH2!+)+SOS1(PRS,PRS) <-> GRB2(SH3!1,SH2!+).SOS1(PRS!1,PRS) kgsp,kgsm


# 1d: Membrane-associated GRB2 binds SOS1 bounds to GRB2
GRB2(SH3,SH2!+)+SOS1(PRS,PRS!1).GRB2(SH3!1,SH2) <-> GRB2(SH3!2,SH2!+).SOS1(PRS!2,PRS!1).GRB2(SH3!1,SH2) kxgsp,kxgsm

# 1e: Free GRB2 binds membrane-associated SOS1
GRB2(SH3,SH2)+SOS1(PRS,PRS!1).GRB2(SH3!1,SH2!+) <-> GRB2(SH3!2,SH2).SOS1(PRS!2,PRS!1).GRB2(SH3!1,SH2!+) kxgsp,kxgsm

# 1f: Membrane-associated GRB2 binds membrane-associated SOS1
GRB2(SH3,SH2!+)+SOS1(PRS,PRS!1).GRB2(SH3!1,SH2!+) <-> GRB2(SH3!2,SH2!+).SOS1(PRS!2,PRS!1).GRB2(SH3!1,SH2!+) kxgspsr,kxgsmsr
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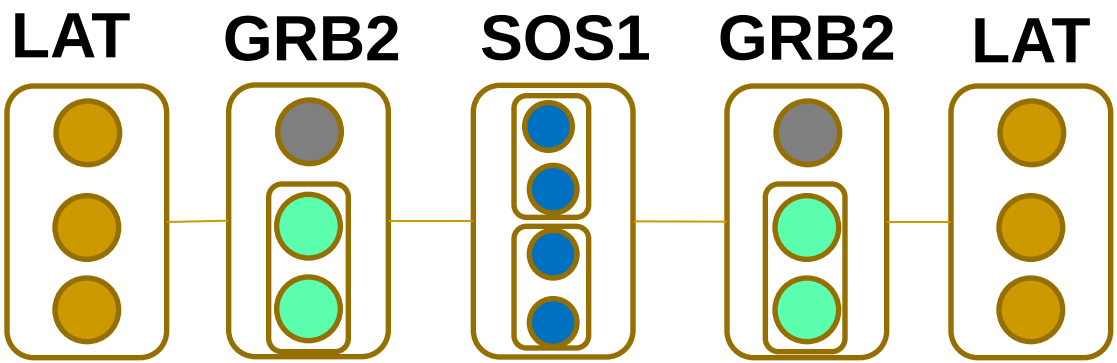
Rule-based Model for LAT



Binding of pLAT with GRB2 and SOS1

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# 2a: LAT binds free GRB2
LAT(Y~P)+GRB2(SH2,SH3) <-> LAT(Y~P!1).GRB2(SH2!1,SH3) kglp,kglm

# 2b: monoLAT binds GRB2 bound to SOS1
LAT(Y~P)+GRB2(SH2,SH3!1).SOS1(PRS!1,PRS) <-> LAT(Y~P!2).GRB2(SH2!2,SH3!1).SOS1(PRS!1,PRS) kglp,kglm

# 2c: LAT binds membrane-associated GRB2
LAT(Y~P)+GRB2(SH2,SH3!1).SOS1(PRS!1,PRS!2).GRB2(SH2,SH3!2) <-> LAT(Y~P!3).GRB2(SH2!3,SH3!1).SOS1(PRS!1,PRS!2).GRB2(SH2,SH3!2) kglp,kglm

# 2d: LAT binds membrane-associated GRB2
LAT(Y~P)+GRB2(SH2,SH3!1).SOS1(PRS!1,PRS!2).GRB2(SH2!3,SH3!2).LAT(Y~P!3) <-> LAT(Y~P!4).GRB2(SH2!4,SH3!1).SOS1(PRS!1,PRS!2).GRB2(SH2!3,SH3!2).LAT(Y~P!3) kxglp,kxglm
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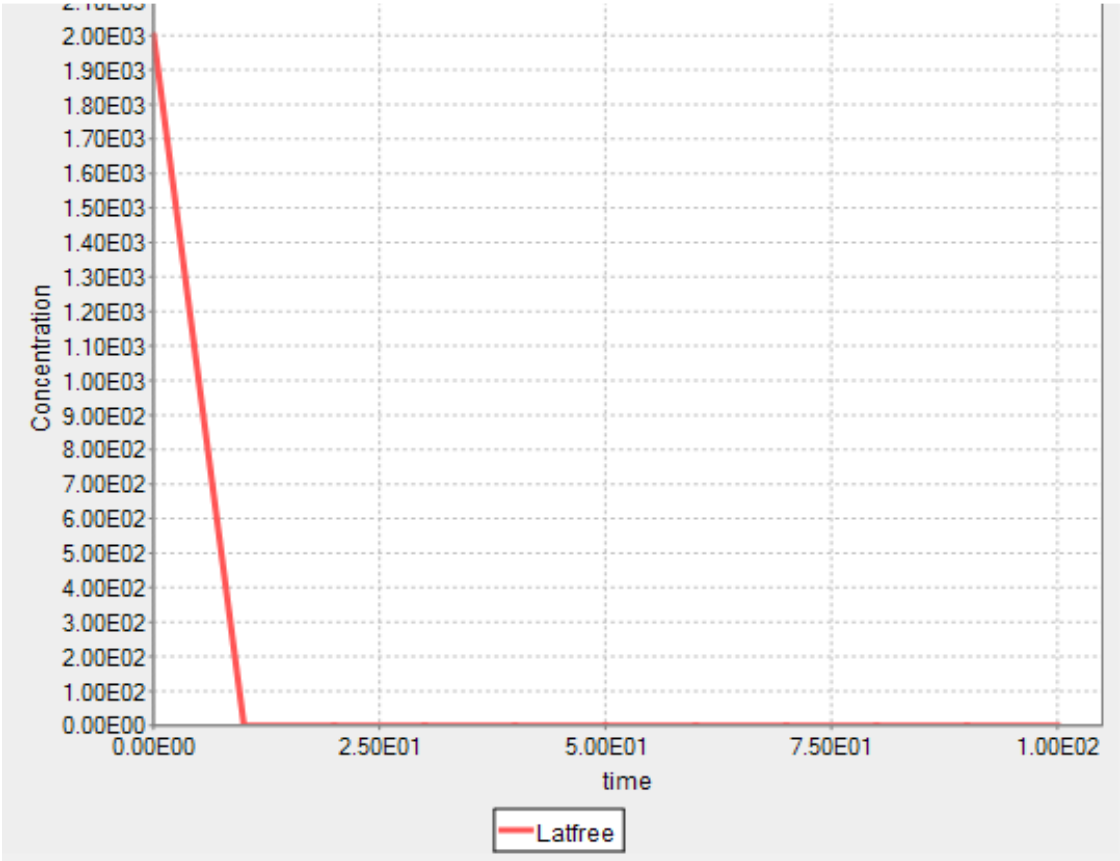
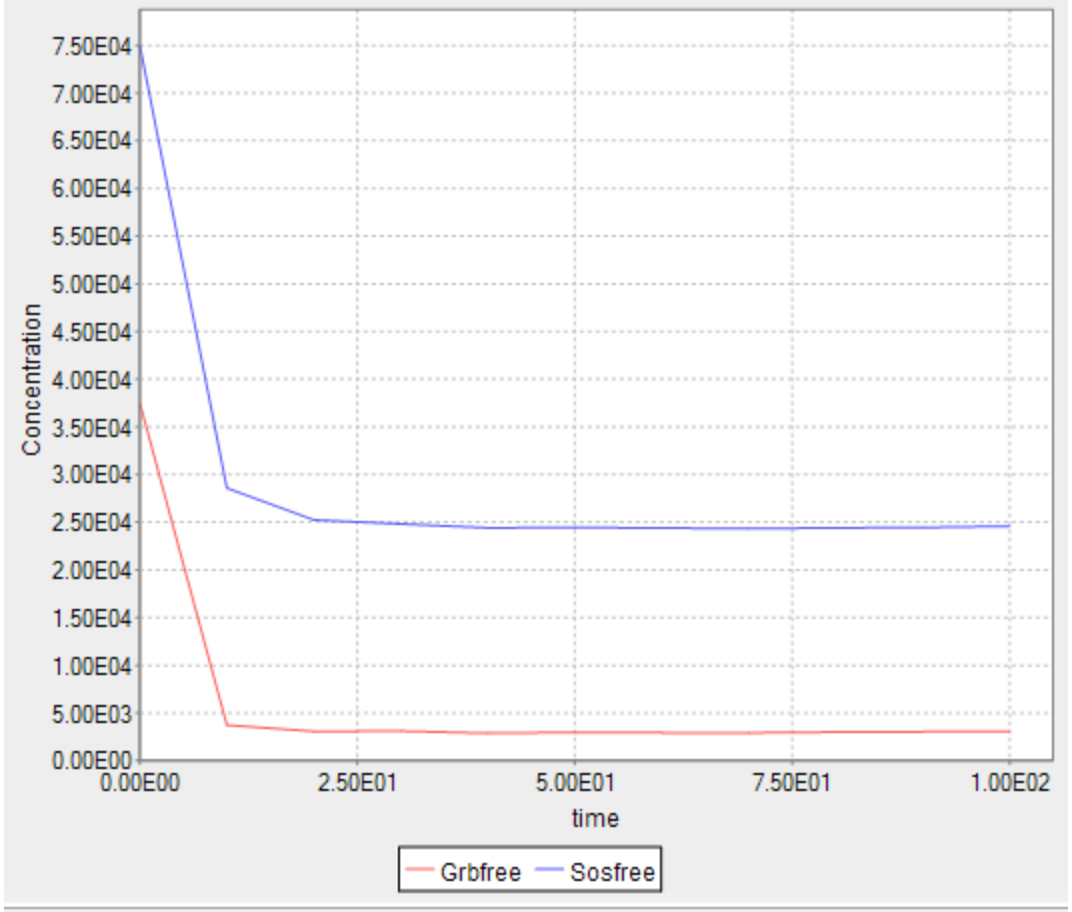
Preliminary Results

Species LATfree (LAT(Y~U,Y~U,Y~U))



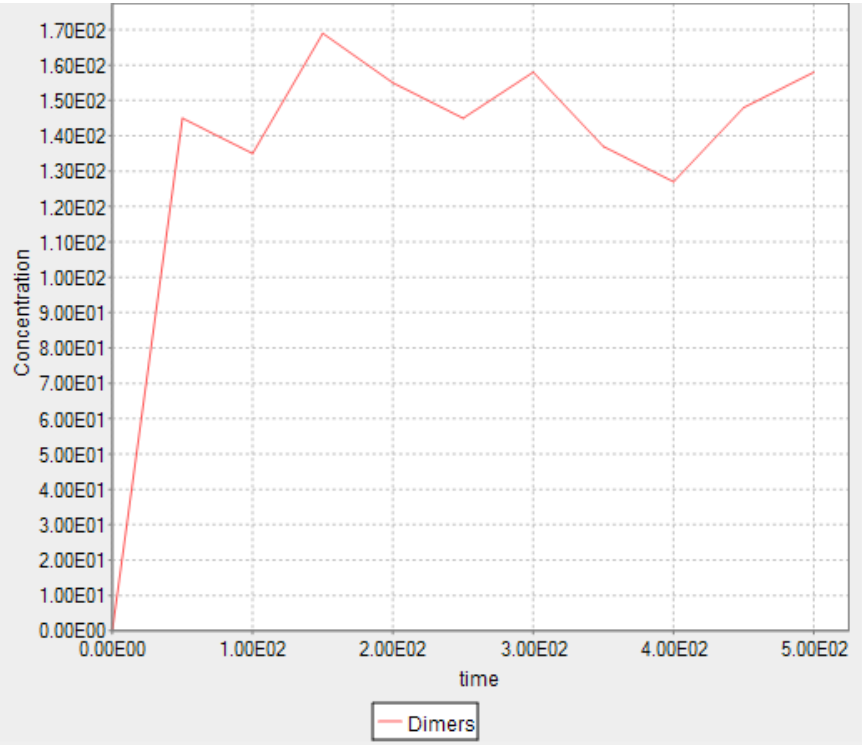
Preliminary Results

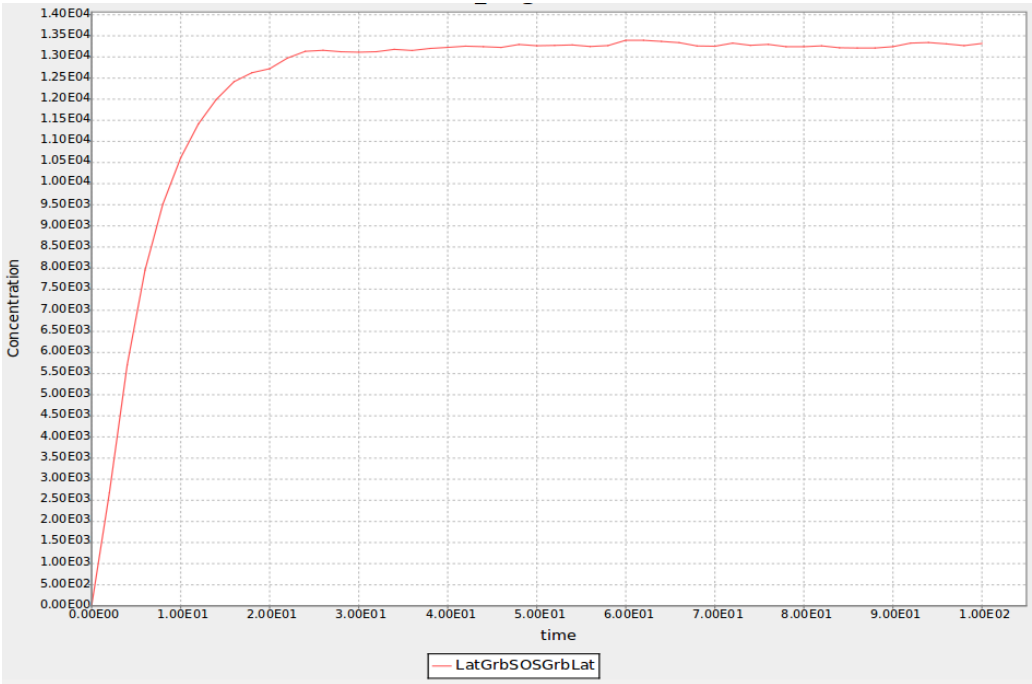
- Species GRB2free (GRB2(SH2,SH3))
- Species SOS1free (SOS1(PRS,PRS))



Preliminary Results

Aggregate with two LAT molecules

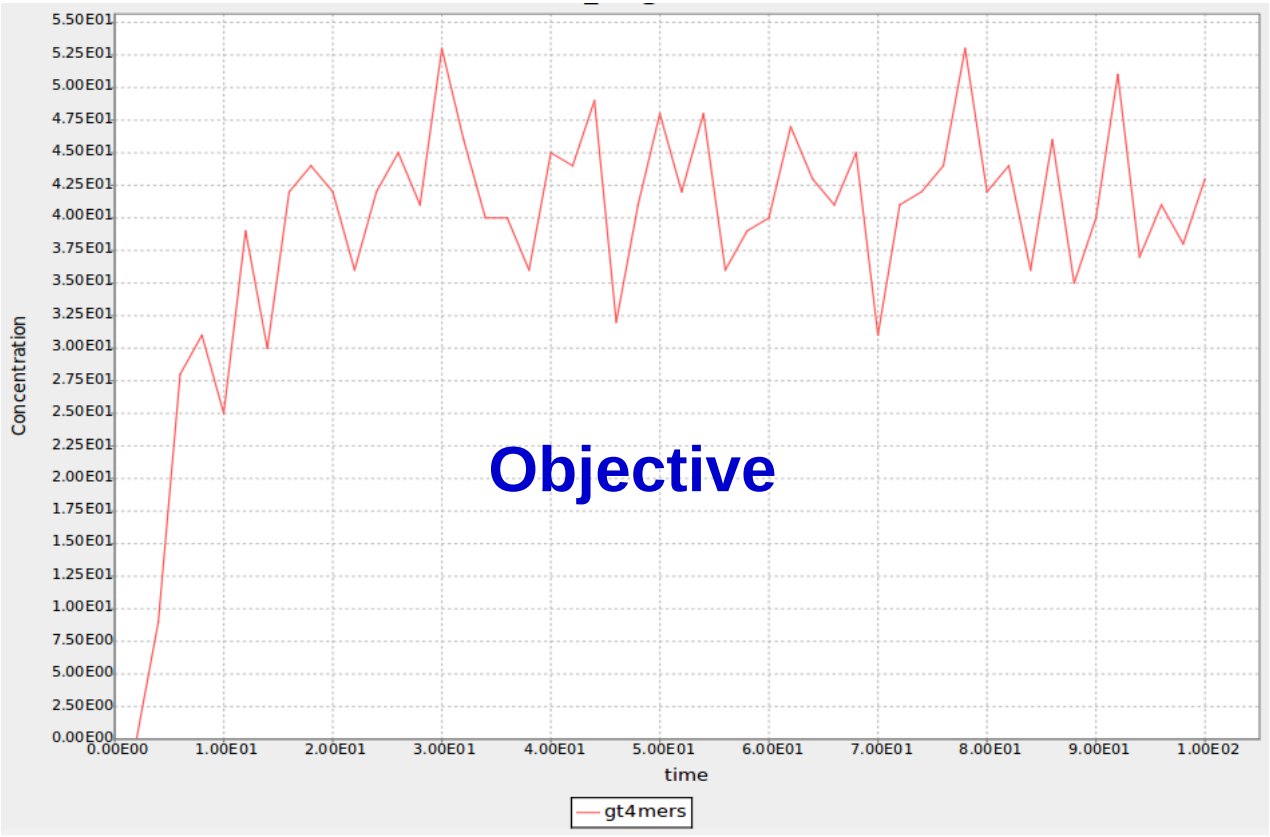




Source code taken from (http://public.tgen.org/dynstoc/download/models/lat.bngl, DYNSTOC: a tool for simulating large-scale rule-based models)

Preliminary Results

Aggregate with more than four LAT molecules



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DYNSTOC: a tool for simulating large-scale rule-based models)

Conclusion

•Rule-based modeling allows the formalization of mechanistic hypothesis.

•A useful mechanistic modeling based on local interactions.

•Allows the construction of abstract models that can be gradually refined.

•Currently, we have achieved to produce LAT aggregates with only two LAT molecules.

•If phosphorylation code, and aggregation code are run separately, the produce results that verifies the hypothesis of LAT phosphorylation and aggregation respectively.

Thanks

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