

Abduction and induction for modelling
inhibition
in metabolic networks

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Overview

Background and motivation

A logic-based framework for modelling inhibition

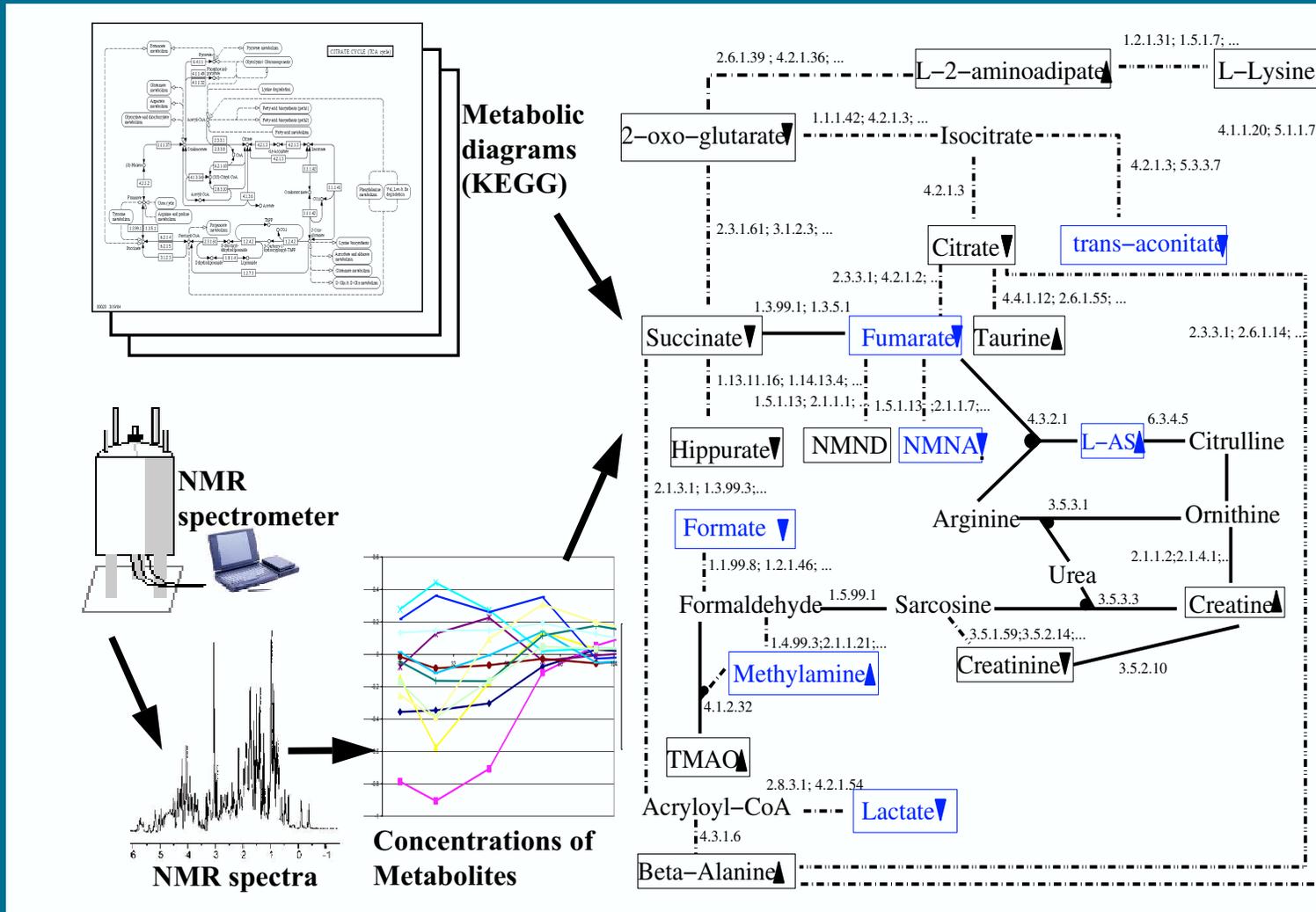
Using Progol 5.0 for:

abduction of ground hypotheses

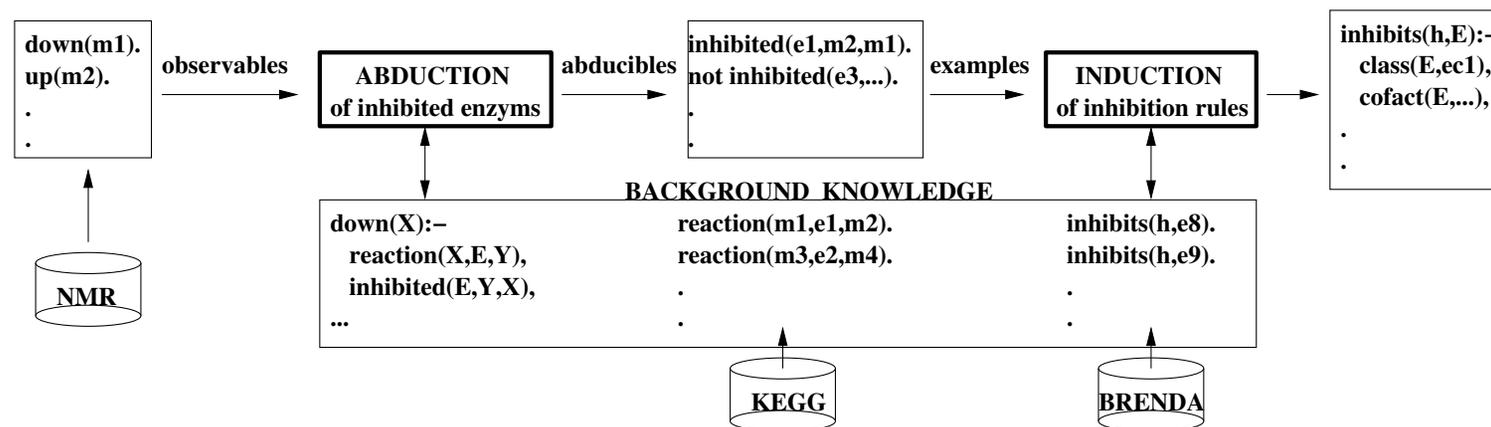
induction of non-ground hypotheses

Conclusion

Metabolic network affected by Hydrazine



An Abductive/Inductive framework for modelling inhibition



Examples of hypotheses

Ground hypotheses:

```
inhibited('2.6.1.39',true,'12aminoadipate','2oxoglutarate',8).
inhibited('2.3.1.61',false,'2oxoglutarate','succinate',8).
inhibited('1.13.11.16',false,'succinate','hippurate',8).
inhibited('2.6.1.-',true,'taurine','citrate',8).
inhibited('4.1.2.32',true,'methylamine','tmao',8). ...
```

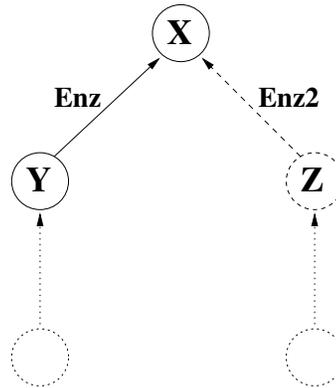
Enzyme classifications (BK):

```
eclass('2.6.1.39', 'aminotransferase').
eclass('2.6.1.-', 'aminotransferase'). ...
```

Non-ground hypotheses:

```
inhibited(Enz, true, M1, M2, T):-
    reactionnode(M2,Enz,M1),
    eclass(Enz,'aminotransferase').
```

A simple temporal model for down-regulation

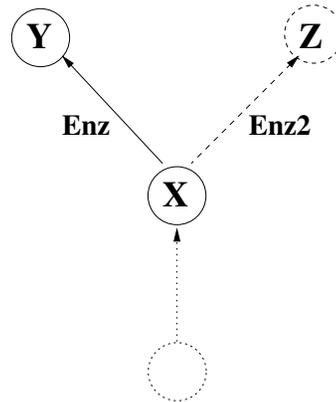


```
concentration(X,down,T):-  
  reactionnode(X,Enz,Y),  
  inhibited(Enz,Y,X,T).
```

```
concentration(X,down,T):-  
  reactionnode(X,Enz,Y),  
  not(inhibited(Enz,Y,X,T)),  
  concentration(Y,down,T).
```

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A simple temporal model for up-regulation

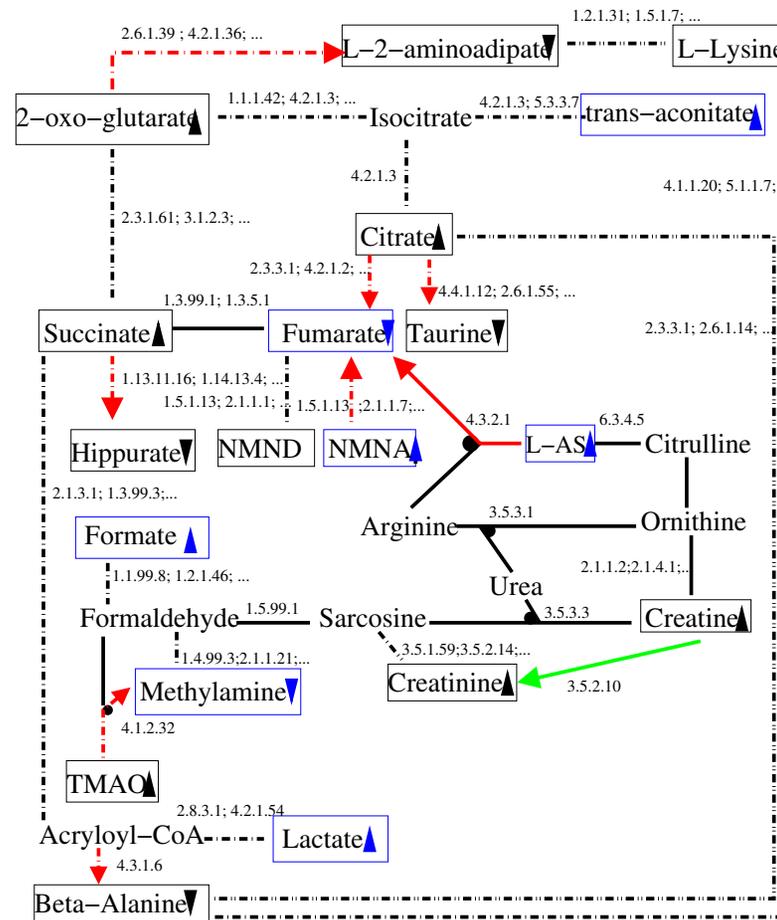


```
concentration(X,up,T):-  
  reactionnode(Y,Enz,X),  
  inhibited(Enz,X,Y,T).
```

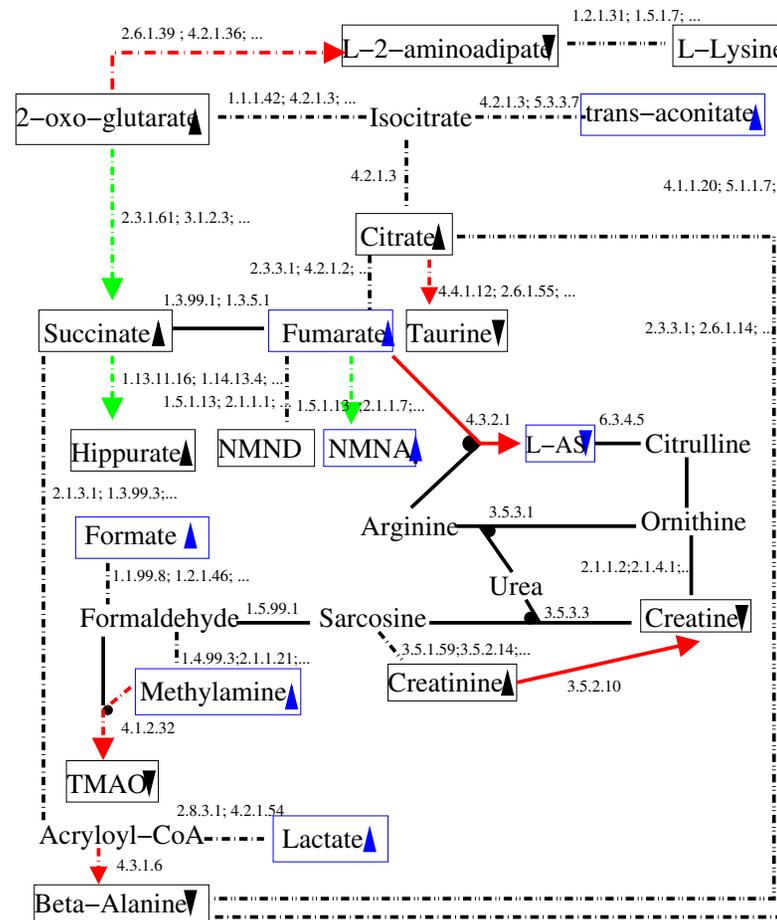
```
concentration(X,up,T):-  
  reactionnode(X,Enz,Y),  
  not(inhibited(Enz,Y,X,T)),  
  concentration(Y,up,T).
```

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Examples of ground hypotheses - 48 hrs



Examples of ground hypotheses - 72 hrs



Null hypothesis examined in the Experiments

Generalising ground hypotheses does not lead to increased predictive accuracy.

Experimental method

```
for  $t$  in (8hrs, 24hrs, 48hrs, 72hrs, 96hrs) do
  for  $j=1$  to  $n$  do
     $Ts_{tj}$  = a randomly selected example from  $E_t$ 
     $Tr_{tj} = E_t - Ts_{tj}$ 
    for  $i$  in (4,9,14,19) do
       $Tr_{tji} = i$  training example randomly sampled from  $Tr_{tj}$ 
    end
  end
end
end
for  $t$  in (8hrs, 24hrs, 48hrs, 72hrs, 96hrs) do
  for  $j=1$  to  $n$  do
    for  $i$  in (4,9,14,19) do
       $H_{tji}$  = learned hypotheses using the training set  $Tr_{tji}$ 
       $A_{tji}$  = predictive accuracy of  $H_{tji}$  on the test set  $Ts_{tj}$ 
    end
  end
end
end
for  $i$  in (4,9,14,19) do
  Plot average of  $A_{tji}$  versus  $i$  ( $j \in [1..n]$  and  $t \in [8, 24, 48, 72, 96]$ )
*  $E_t$  is the set of examples at time  $t$  and  $n = |E_t| = 20$ 
```

Evaluating hypotheses

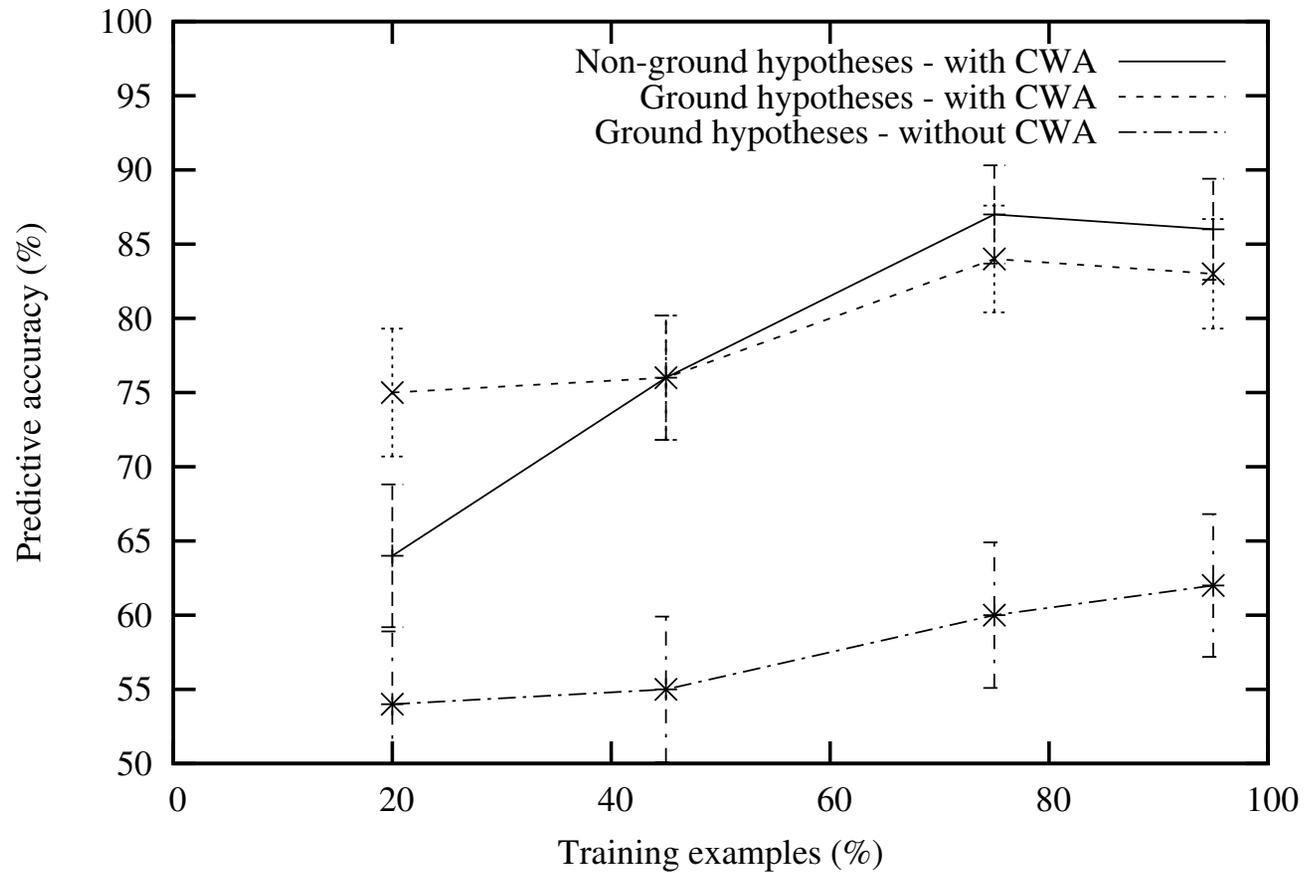
Closed World Assumption(CWA):

```
inhibited(Enz,false,X,Y,T):-  
    reactionnode(Y,Enz,X),  
    not(inhibited(Enz,true,_,_,T)).
```

Test Predicate:

```
concentration1(X,up,T):-  
    concentration(X,up,T),  
    not(concentration(X,down,T)).  
concentration1(X,down,T).
```

Performance of ground and non-ground hypotheses



* default accuracy : 54%

Summary

- A logic-based model for inhibition which incorporates BK of existing biochemical pathways, inhibitor/enzyme classifications etc.
- Explicit ground hypotheses concerning the inhibitory effect in specific reactions (Abduction)
- Increased predictive accuracy when ground hypotheses are generalised (Induction)

Further work

- Evaluating the model on different NMR data (work in progress)
- Extending the model to include other aspects in addition to biochemistry (e.g. physiology)
- Enhancing the representation (e.g. quantitative hypotheses)