Rule-Based Modeling of Biochemical Networks with BioNetGen2

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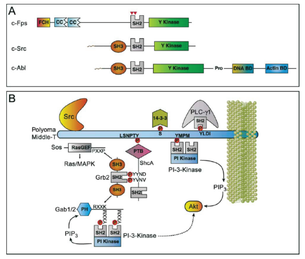
cellsignaling.lanl.gov

Introduction

Signaling Proteins are Modular and Form an Array of Distinct Complexes



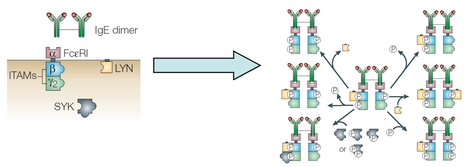
T. Pawson, Cell (2004)

Combinatorial Complexity

The modular structure of signaling proteins gives rise to an exponentially exploding number of distinct chemical species and reactions.

Poses a major barrier to modeling and understanding the dynamics of signaling and other biochemical networks.

Example. Four protein components of the FcεRI signaling pathway give rise to a large network of species and reactions

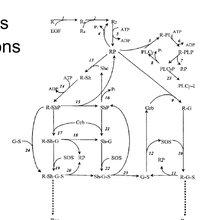


354 species / 3680 reactions

Common modeling approaches limit complexity by making implicit assumptions.

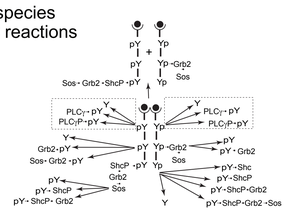
Example. Two models of early events in EGFR signaling.

18 species
34 reactions



Kholodenko et al., J. Biol. Chem. (1999)

356 species
3749 reactions

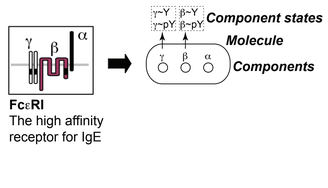


Blinov et al., BioSyst. (2005)

Graphical Rule-Based Modeling Approach

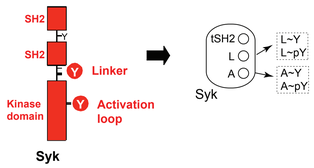
Signaling Proteins and Their Complexes are Represented as Graphs

A multi-subunit receptor

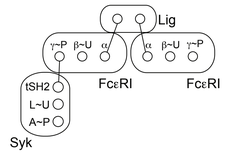


FcεRI
The high affinity receptor for IgE

A kinase that binds receptor

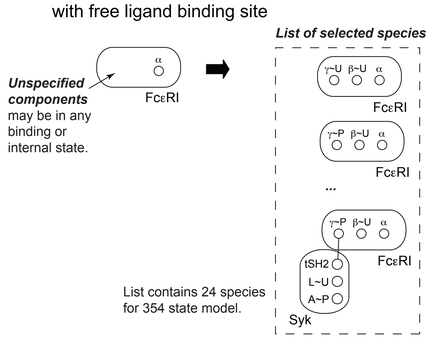


A molecular complex

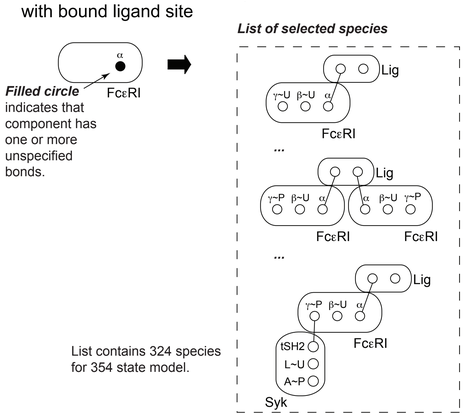


Graphical Patterns Select Groups of Chemical Species with Specified Attributes

A pattern that selects a receptor with free ligand binding site

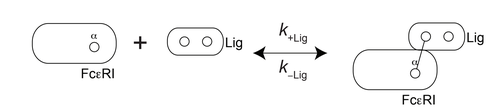


A pattern that selects a receptor with bound ligand site

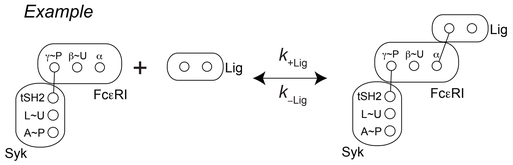


Reaction Rules Serve as the Generators of Chemical Species and Reactions

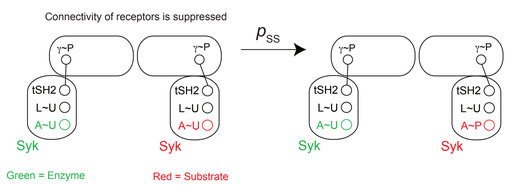
Ligand binding (48 reactions)



Example

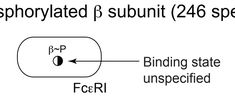


Syk transphosphorylation (64 reactions)

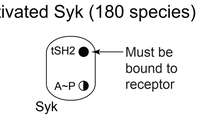


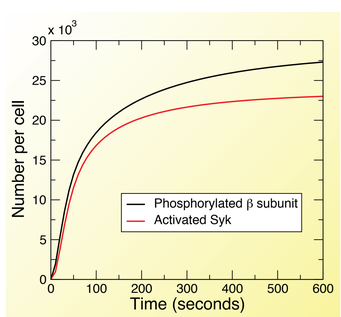
Patterns are Used to Define Observable Outputs

Phosphorylated β subunit (246 species)



Activated Syk (180 species)





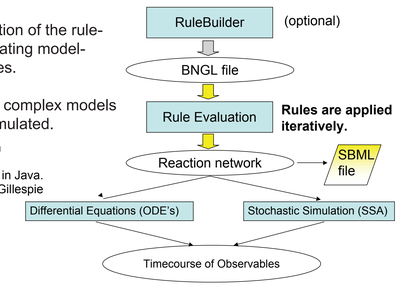
BioNetGen2 Software

Overview

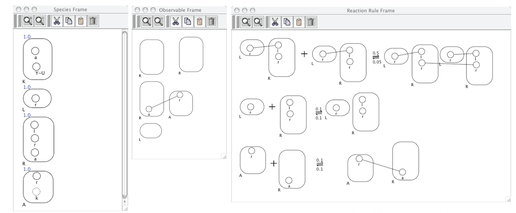
Provides a complete implementation of the rule-based modeling approach, integrating model-building and simulation capabilities.

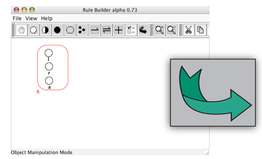
Using these tools, very large and complex models can be easily constructed and simulated.

- **BNG2.pl –** Graph parser / Rule evaluation backend written in Perl (prototype).
- **RuleBuilder –** Graphical front end written in Java.
- **Network –** ODE (based on CVODE) and Gillespie simulation code written in C.



A Simple Example





BNGL input file

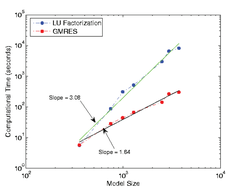
```
begin parameters
1  kp1  1e-2
2  km1  1e-2
3  kp2  6e-3
4  km2  5e-2
5  kpA  5e-4
6  kmA  1e-1
end parameters

begin species
1  L(r)      10
2  R(l,r,a)   1
3  A(r,k)   0.5
end species

begin reaction rules
1  L(r) + R(l,r) <-> L(r!1).R(l!1,r) kp1,km1
2  L(r!1).R(l!1,r) + L(r!1).R(l!1,r) <->
L(r!1).R(l!1,r!3).L(r!2).R(l!2,r!3) kp2,km2
3  A(r) + R(a) <-> A(r!1).R(a!1) kpA,kmA
end reaction rules

begin observables
1  Molecules R_dim   R.R
2  Molecules A_bound A(r!1).R(a!1)
3  Molecules L_tot   L
end observables

generate_network({});
simulate_ode({t_end=>100,n_steps=>50});
```

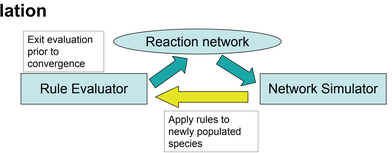
BNG2.pl output

```
BioNetGen version 2.0.14+
Read 6 parameters.
Read 3 species.
Read 3 reaction rule(s).
Read 3 observable(s).
command: generate_network({});
max_iter=100
max_agg=1e+99
check_iso=1
Iteration   0:     3 species      0 rxns
Iteration   1:     5 species      2 rxns
Iteration   2:     7 species      7 rxns
Iteration   3:     9 species     13 rxns
Iteration   4:     9 species     18 rxns
Group R_dim contains 3 elements.
Group A_bound contains 4 elements.
Group L_tot contains 6 elements.
Wrote network to example1.net.
CPU TIME: generate_network 0.2 s.
```

Simulation Capabilities

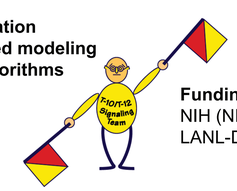
- **Very large systems of ODEs (>10⁴)**
- **Adaptive network generation for Gillespie simulation**





Future Work

- **Improve efficiency of rule evaluation**
- **Propose standards for rule-based modeling**
- **Improve adaptive simulation algorithms**
- **More applications**



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LANL-DOE

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