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Progress report: SBML Level 3 package "FBA"

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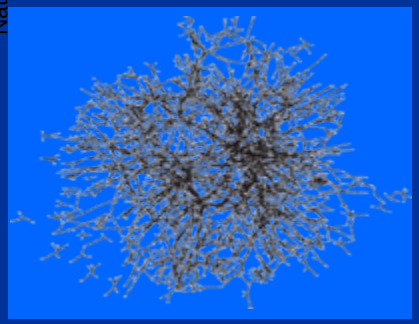

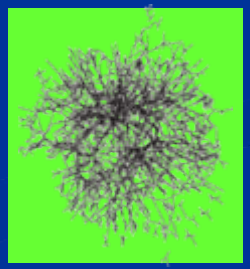

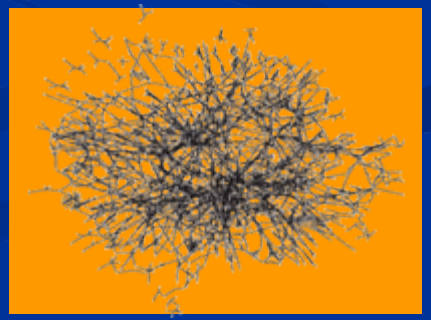

COMBINE 2010 Edinburgh, Scotland

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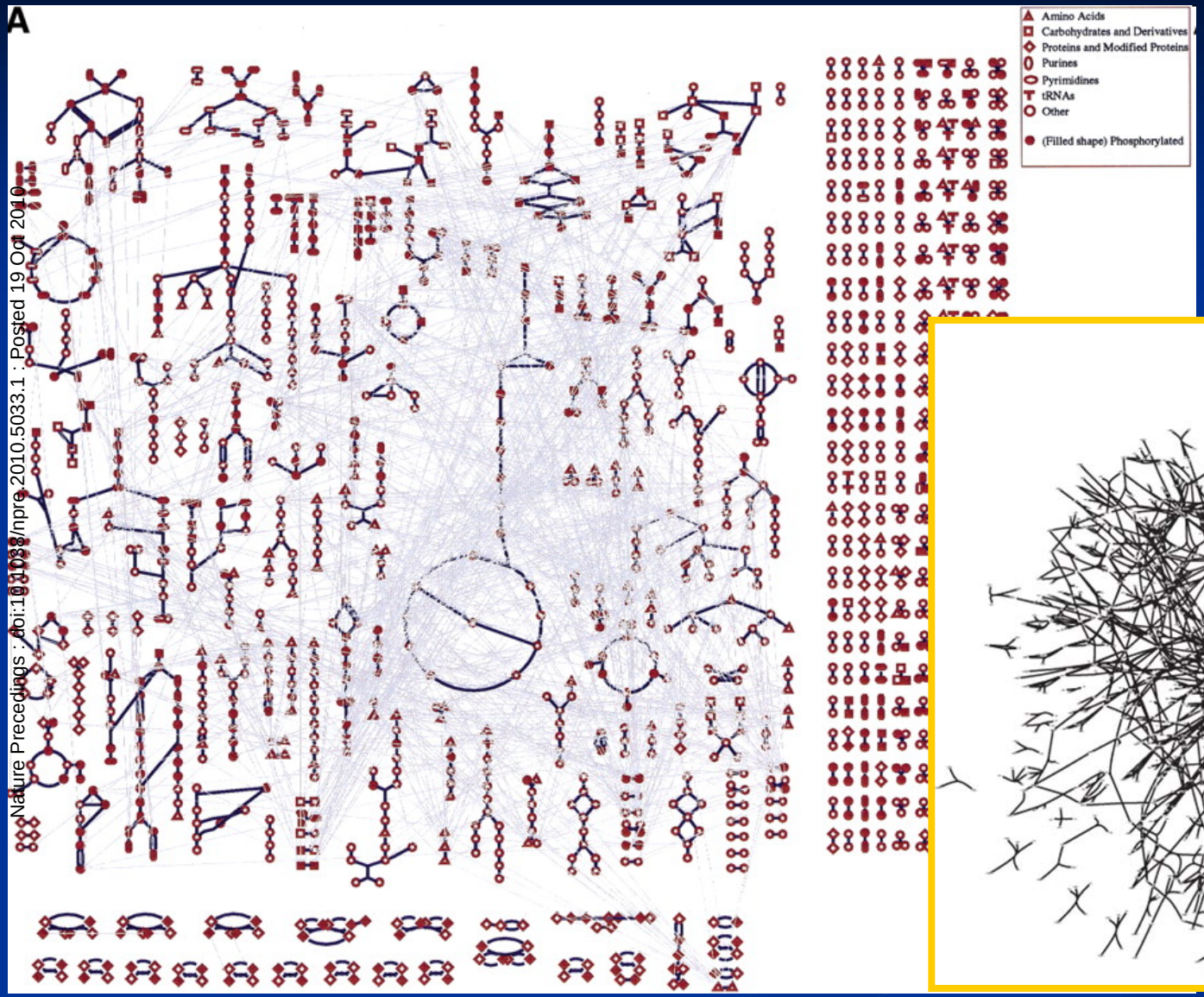
Background

Initial draft 2010

First revision and beyond

Eschericha coli metabolic network



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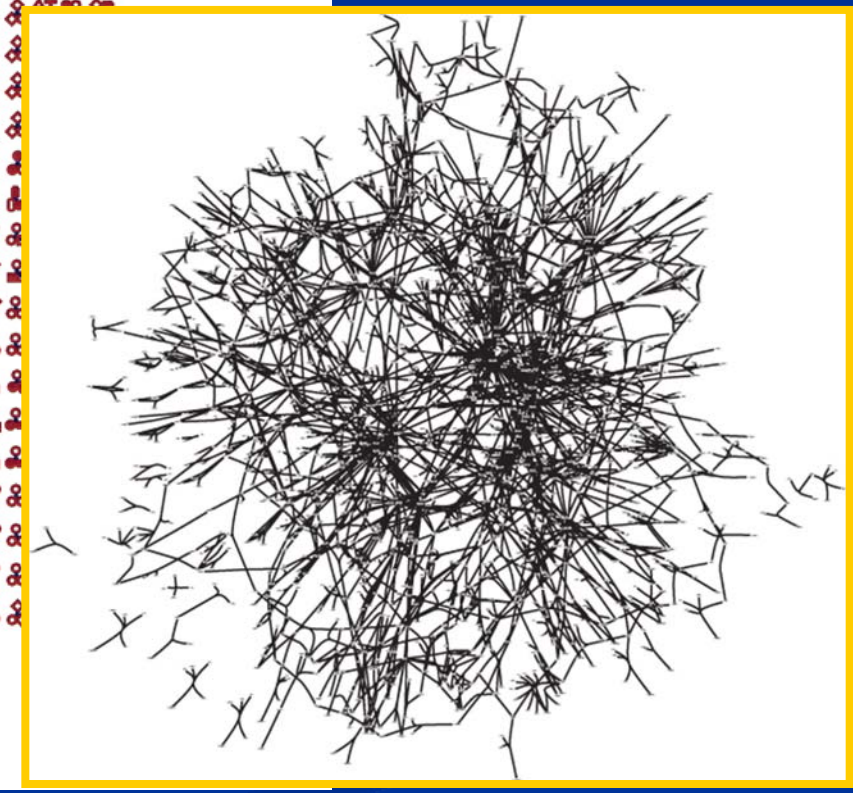


Ouzounis et al. *Genome Res. 2000. 10: 568-576*

Vallabhajosyula et al. Bioinformatics 2006 22:346-353

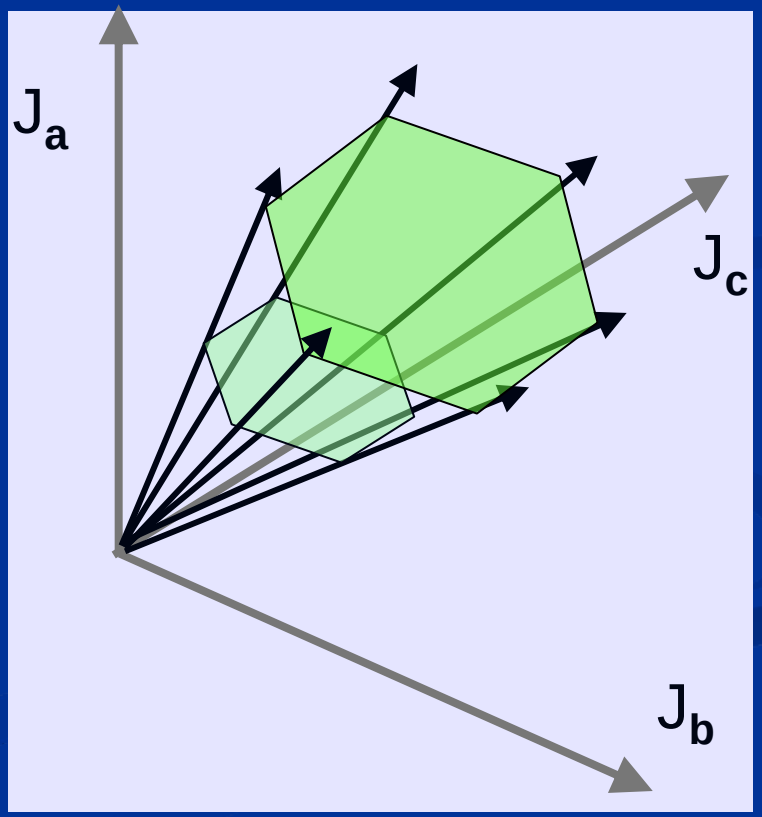
Flux balance analysis

- Optimise a specific property: typically biomass production
- Constrained by the stoichiometry (N)

Maximize
biomass

Subject to
NJ = 0

With bounds
0 <= J_{irrev} <= inf
-inf <= J_{rev} <= inf
l.b <= Jn <= u.b



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1st ideas Karthik Raman 2005

Critical points

- FBA is an *operation* performed on a model, essentially specified by the objective function, unlike a kinetic model *definition*
  - Flux bounds may be biochemical constraints on the model (or based on the simulation)
- ***Fundamental question***: should SBML also allow
  - exchange of simulation results (flux values), esp. for FBA?
  - Specification of a model *instance*, in terms of a particular objective function

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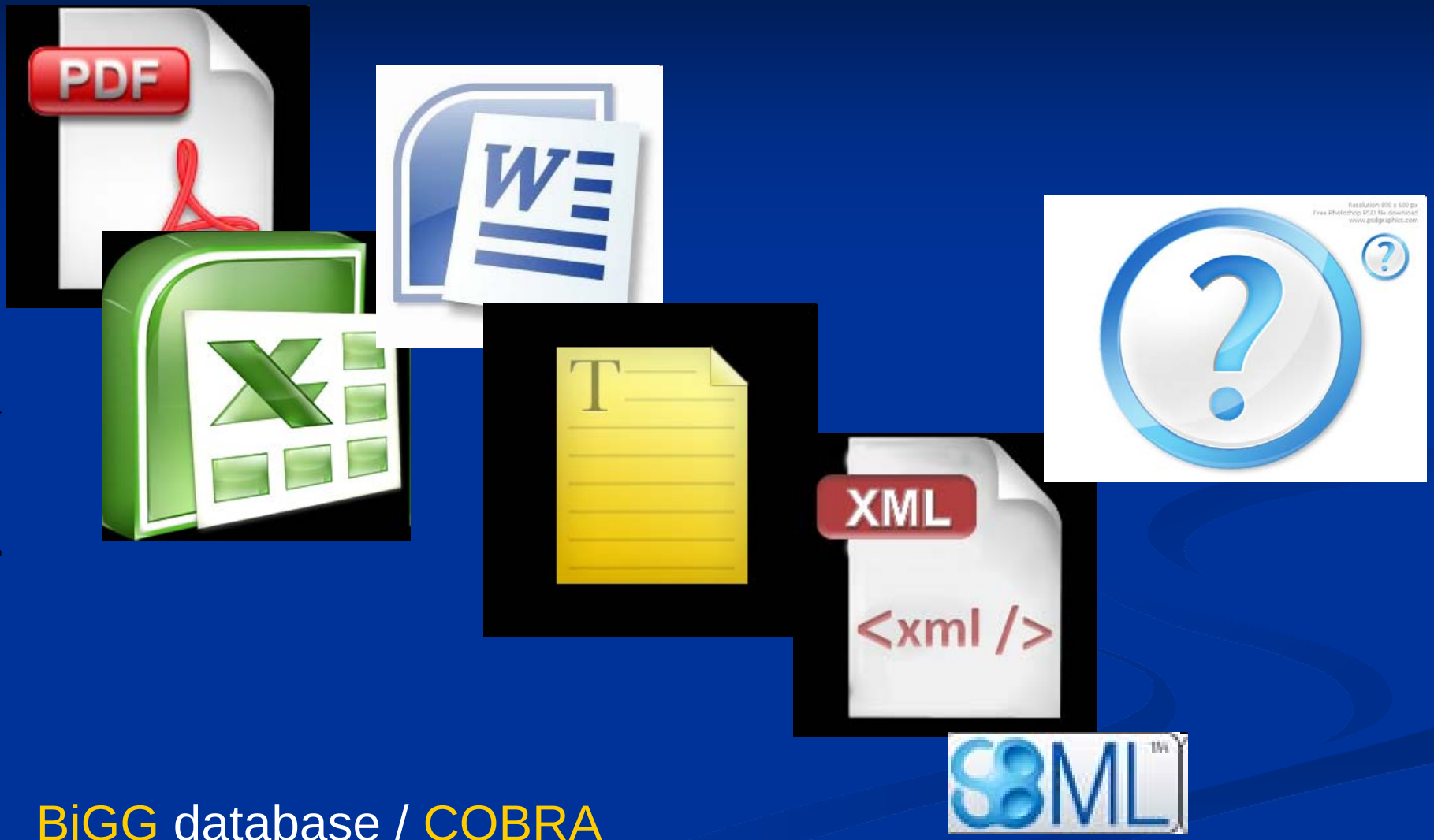
Genome scale models



- BiGG database / COBRA
  - uses SBML L2

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Genome reconstructions 2009

Available reconstructions (all formats): 55+ **

BiGG database (http://bigg.ucsd.edu/) 10 GSR's (COBRA)

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nature biotechnology

Nature Biotechnology 28 (9) , pp 977–982, September 2010

2010

High-throughput generation, optimization and analysis of genome-scale metabolic models

Christopher S Henry[1], Matthew DeJongh[2], Aaron A Best[3], Paul M Frybarger[2,3], Ben Linsay[4] & Rick L Stevens[4,5]

Genome-scale metabolic models have proven to be valuable for predicting organism phenotypes from genotypes. Yet efforts to develop new models are failing to keep pace with genome sequencing. To address this problem, we introduce the Model SEED, a web-based resource for high-throughput generation, optimization and analysis of genome-scale metabolic models. The Model SEED integrates existing methods and introduces techniques to automate nearly every step of this process, taking ~48 h to reconstruct a metabolic model from an assembled genome sequence. We apply this resource to generate 130 genome-scale metabolic models representing a taxonomically diverse set of bacteria. Twenty-two of the models were validated against available gene essentiality and Biolog data, with the average model accuracy determined to be 66% before optimization and 87% after optimization.

** A.M. Feist, M.J. Herrgard, I. Thiele, J.L. Reed, B.Ø. Palsson Nat. Rev. Microbiol. 2009 Feb;7(2):129-43.

Nature Precedings : doi:10.1038/npre.2010.5033.1 : Posted 19 Oct 2010

Background

Initial draft 2010

First revision and beyond

SBML^3 FBA

- Extends SBML by adding classes for flux bounds and objective functions
- Implemented as an SBML L2V4 annotation

```
<?xml version="1.0" encoding="utf-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1" >
 <model id="BranchMultipleCycle" name="BranchMultipleCycle">
  <annotation>
   <fba:fluxBalance xmlns:fba="http://www.sbml.org/sbml/level3/version1/fba/version1
    <fba:listOfConstraints>
     <fba:constraint fba:reaction="J0" fba:operation="equal" fba:value="10" />
    </fba:listOfConstraints>
   <fba:listOfObjectives fba:activeObjective="obj1">
    <fba:objective id="obj1" fba:type="maximize">
     <fba:listOfFluxes>
      <fba:fluxObjective fba:reaction="J8" fba:coefficient="1" />
     </fba:listOfFluxes>
    </fba:objective>
   </fba:listOfObjectives>
  </fba:fluxBalance>
</annotation>
```

Bergmann, Frank and Olivier, Brett. (2010) *SBML Level 3 Package Proposal: Flux.* Nature Precedings <http://dx.doi.org/10.1038/npre.2010.4236.1>

Nature Precedings : doi:10.1038/npre.2010.5033.1 : Posted 19 Oct 2010

SBML^3 FBA

- Implemented as SBML L2 extension :
  - Systems Biology WorkBench (www.sys-bio.org)

  - PyscesCBM (pysces.sourceforge.net)

  - ConverterTool (Converts BiGG/COBRA into L2 + FBA extension)

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Flux Bounds

Bounds a model flux (SBML reaction) with a value.

Multiple bounds on single reaction possible.

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```
<listOfFluxBounds>

<fluxBound id="fb1" reaction="Glc_in"
  operation="lessEqual" value="10"/>

<fluxBound id="fb2" reaction="R_HEX1"
  operation="greaterEqual" value="0"/>

</listOfFluxBounds>
```

Objective function

Defines one or more optimization targets.

```
<listOfObjectives activeObjective="ObjFun1">

<objective id="ObjFun1“ type="maximize">
 <listOfFluxes>

  <fluxObjective reaction="PFK“ coefficient="1"/>

 </listOfFluxes>
</objective>

</listOfObjectives>
```

Nature Precedings : doi:10.1038/npre.2010.5331.1 : Posted 19 Oct 2010

Extended species

```
<species id="glc"
  name="D-Glucose“
  compartment="Cytosol“
  fba:chemicalEquation=“C6H12O6“
  fba:charge="0“>
```

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- First draft captured the basic model structure but did not deal with annotation.
- Simply left COBRA annotation as is: a reaction <note>

```
<notes>
<html:p>Confidence Level: 0</html:p>
<html:p>SUBSYSTEM: Glycolysis/Gluconeogenesis</html:p>
<html:p>GENE ASSOCIATION: (b3916) or (b1723)</html:p>
…
</notes>
```

- Most important is GENE ASSOCIATION

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Background

Initial draft 2010

First revision and beyond

Species annotation

chemicalEquation replaced with a CHEBI annotation

```
<species metaid="atp" id="atp" name="ATP_C10H12N5O13P3"
 compartment="Cytosol" initialConcentration="1"
 boundaryCondition="true" fba:charge="-4">
      <annotation>
        <rdf:RDF>
          <rdf:Description rdf:about="#atp">
            <bqbiol:is>
              <rdf:Bag>
                <rdf:li
 rdf:resource="urn:miriam:obo.chebi:CHEBI%3A30616"/>
              </rdf:Bag>
            </bqbiol:is>
          </rdf:Description>
        </rdf:RDF>
      </annotation>
    </species>
```

Nature Precedings : doi:10.1038/npre.2010.4282.1 Posted 16 Oct 2010

Gene association

- Add genes to model as boundary species with proper MIRIAM annotation
- Add a listOfGeneAssociations to FBA

```
<listOfGeneAssociations>
   <geneAssociation id="ga3" reaction="R_PFK">
            <association>
              <and>
                <gene>b3916</gene>
                <gene>b1723</gene>
              </and>
            </association>
   </geneAssociation>
</listOfGeneAssociations>
```

Nature Precedings : doi:10.1038/npre.2010.5033.1 : Posted 19 Oct 2010

Open questions / issues

- Now reformat and upload proposal onto sbml.org
- fluxBounds or something more general?
- Objective function and SED-ML
- The best way to deal with gene association?
- Anything else … ?

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- Neil Swainston
- Kieran Smallbone

- Members of:
  - SBML community
  - MEMESA group

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