



# Biological Modeling using APMonitor



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# Overview



- Computational Biology
  - SBML
  - Biomodels Database
- APMonitor
  - Format conversion
  - Simple dynamic models
  - Large scale model
- Conclusions
  - Demo
  - Known Issues/Future development

# Importance of Computational Biology



- Growing area to guide drug development and treatment
- Key to advancement of neuroscience and genome modeling

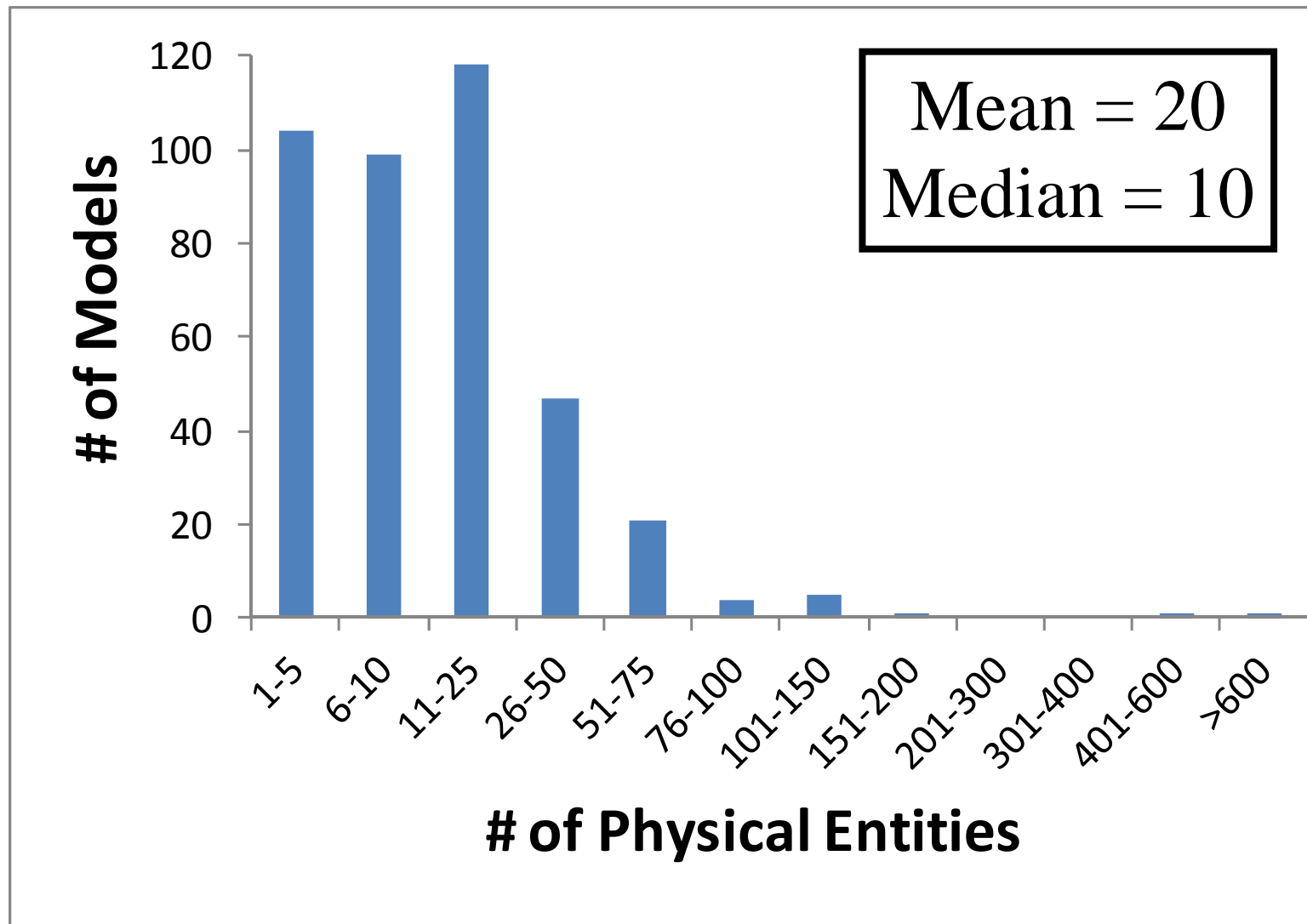


# Systems Biology Markup Language



- Standard format to represent computational biology models
- Based on XML
- Biomodels database has approximately 1000 models in this format
- 200+ software systems support SBML
  - New tool SBMLsimulator by Dr. Dräger
  - <http://www.cogsys.cs.uni-tuebingen.de/software/SBMLsimulator/>

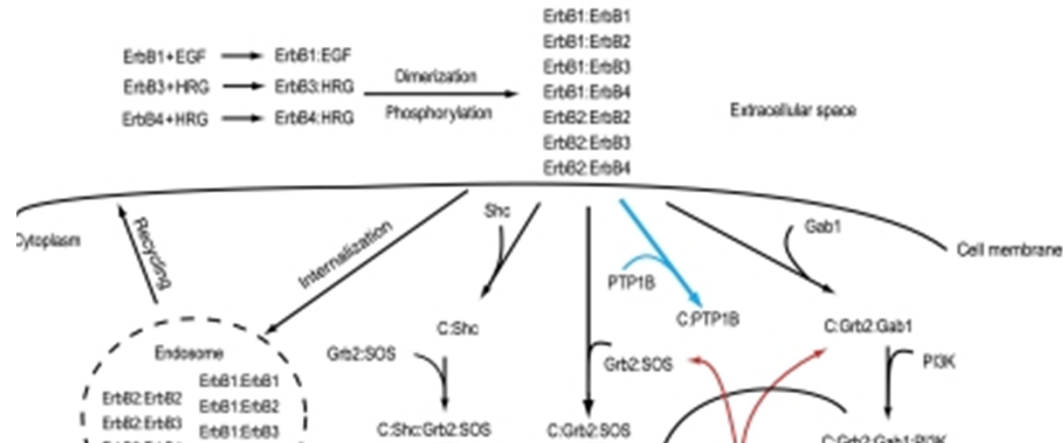
# Biological kinetic models are modestly sized\*



\*Model sizes from 409 curated models in the Biomodels repository (<http://www.ebi.ac.uk/biomodels-main/>)



# Model Size Limited by Tools



*We need better tools (parameter estimation, optimization) to deal with large models!*

- Large ErbB signalling model (~504 physical entities)\*
- Parameter estimation (simulated annealing) took “24 hours on a 100-node cluster computer”

\*Chen et al. [Mol Syst Biol.](#) 2009;5:239 .

# Established Tool, New Application



- **APMonitor used in oil and gas industry**
  - Industrial Automation of Refining and Chemicals
  - Large-scale process models (100,000+ variables)
    - Simulate: Historical data for model validation
    - Estimate: Parameters, disturbances, model structure
    - Optimize: Maximize profit subject to constraints
- **Newly Applied to Computational Biology**

# SBML2APM Conversion Utility



- SBFC-Systems Biology Format Converter
  - SBML2XPP model conversion as a template
  - Similar modeling format
- My Work
  - No prior knowledge of SBML and database programming for 2 years
  - Configuration of SBFC on local system
  - 50 hours of development time to create SBML2APM





# Thoughts on SBFC and JSBML

- Well written template-easy to decipher and manipulate
- Example of the parameter loop

```
// Global Parameters
for (Parameter parameter : parameters) {

    buildIdMap(parameter);

    if (parameter.isConstant()) {
        nbParameters++;
        xppModel +=printConstantParameter(parameter);
    } else {
        xppModel +=printParameter(parameter);
    }
}
}
```

# Simple Example without SBML2APM



## ➤ HIV Virus Simulation

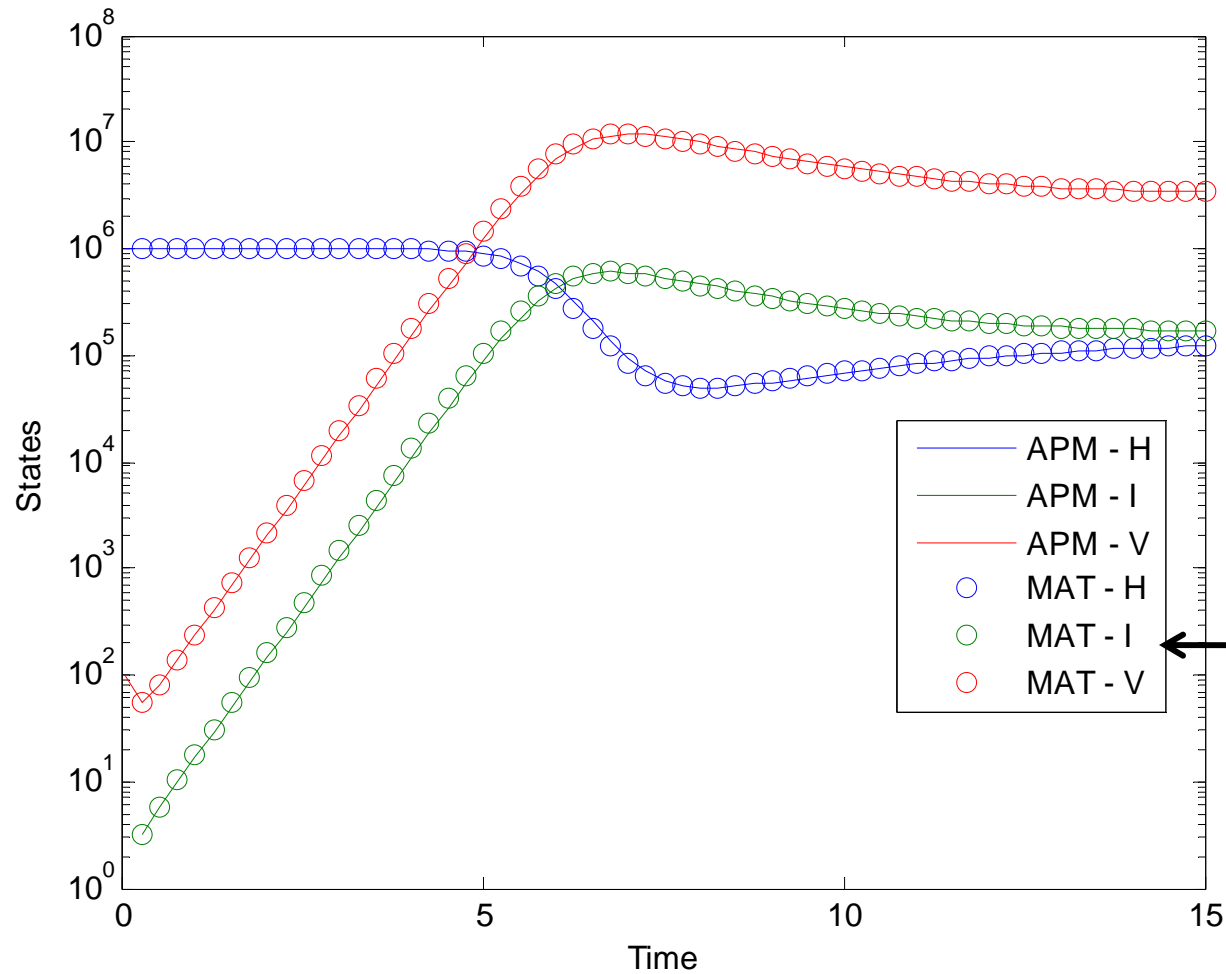
➤ Parameters: 6 →

➤ Variables: 3 →

➤ Equations: 3 →

```
Model
  Parameters
    kr1 = 1e5
    kr2 = 0.1
    kr3 = 2e-7
    kr4 = 0.5
    kr5 = 5
    kr6 = 100
  End Parameters
  Variables
    H = 1e6      ! healthy cells
    V = 1e2      ! virus
    I = 0        ! infected cells
  End Variables
  Equations
    $H = kr1 - kr2*H - kr3*H*V
    $I = kr3*H*V - kr4*I
    $V = -kr3*H*V - kr5*V + kr6*I
  End Equations
End Model
```

# Verification of Dynamic Model



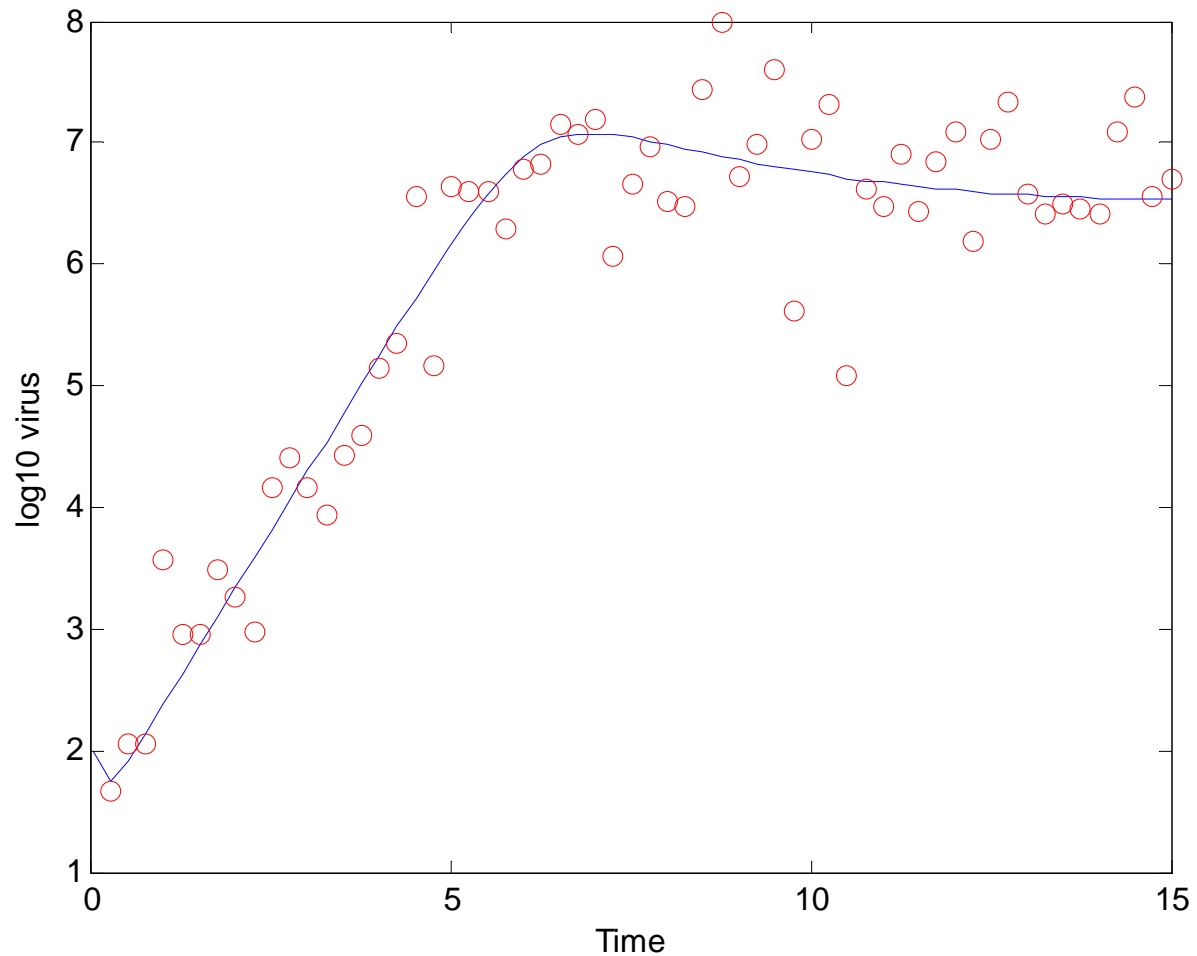
APM Model  
verified with  
MATLAB

MATLAB  
response

# HIV Parameter Estimation



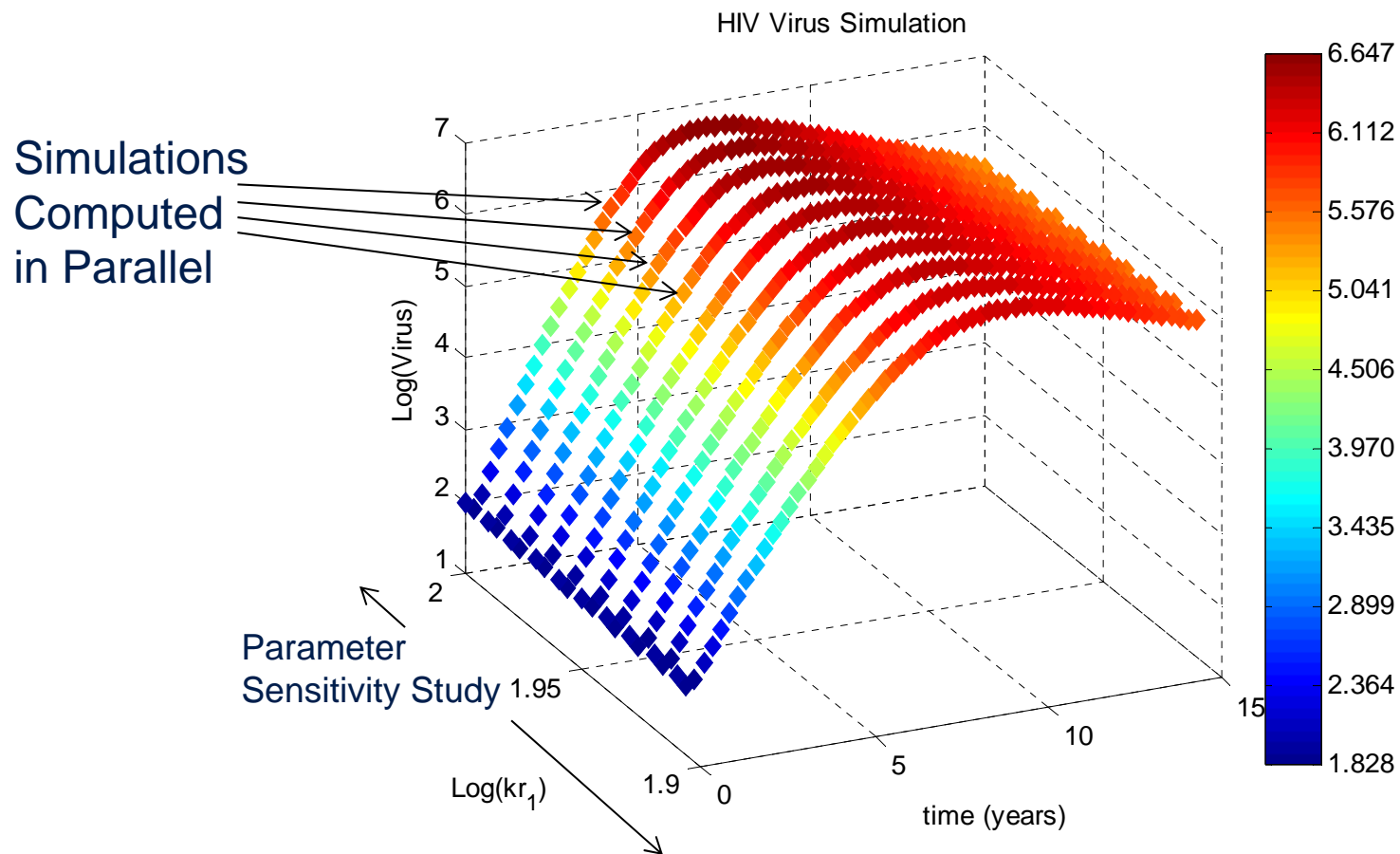
## ➤ Dynamically estimated parameters (6)



# Parallel Processing with APM



- APM MATLAB allows parallel processing



# SBML2APM Converter Limitations

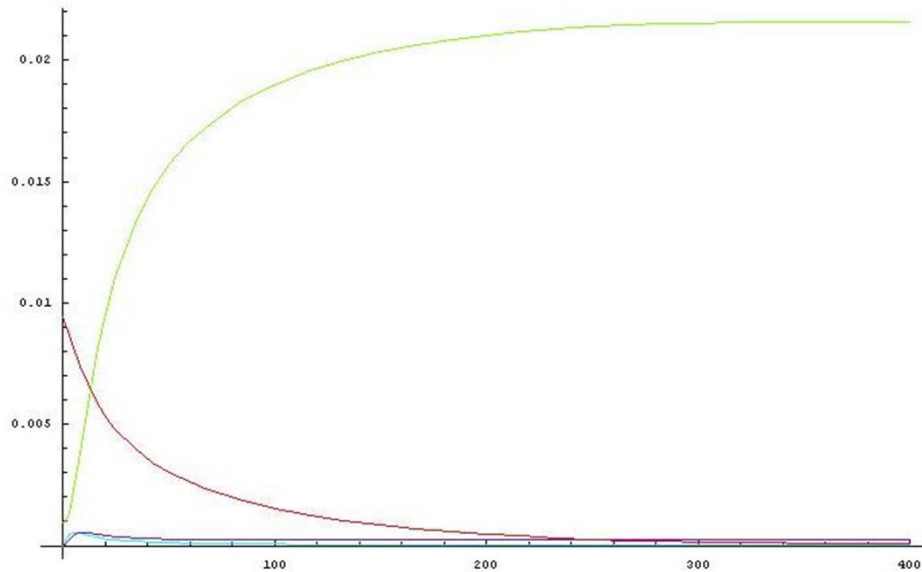


- Some SBML models and data are coupled
  - Piecewise linear functions
  - Logical elements (IF Statements)
- APM separates models and data
  - Model File
    - Equations that describe the system
    - Requires continuous 1<sup>st</sup> and 2<sup>nd</sup> derivatives
  - Scripting and Data Files
    - Change inputs at various times
    - Include logical arguments (IF Statements)

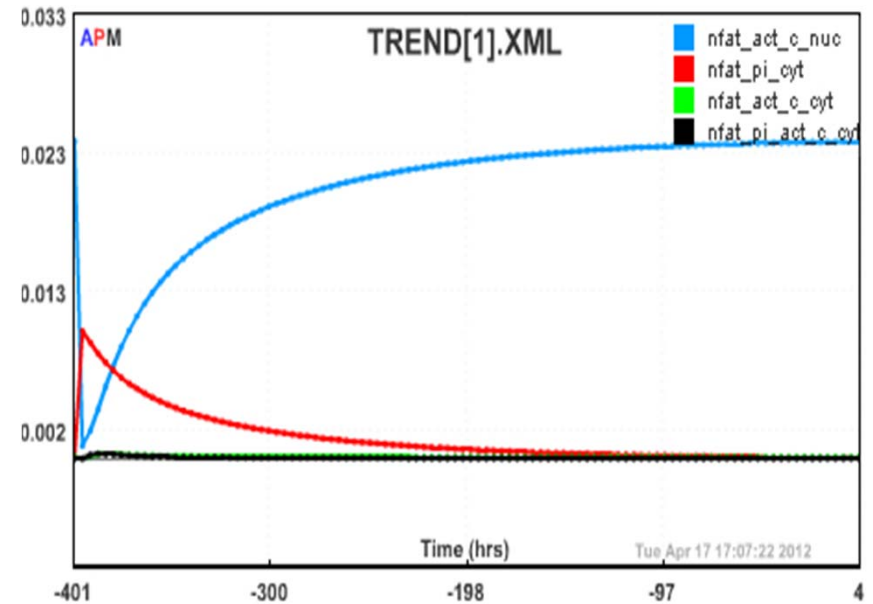
# Examples: Fisher2006\_NFAT\_Activation



## Curated Model

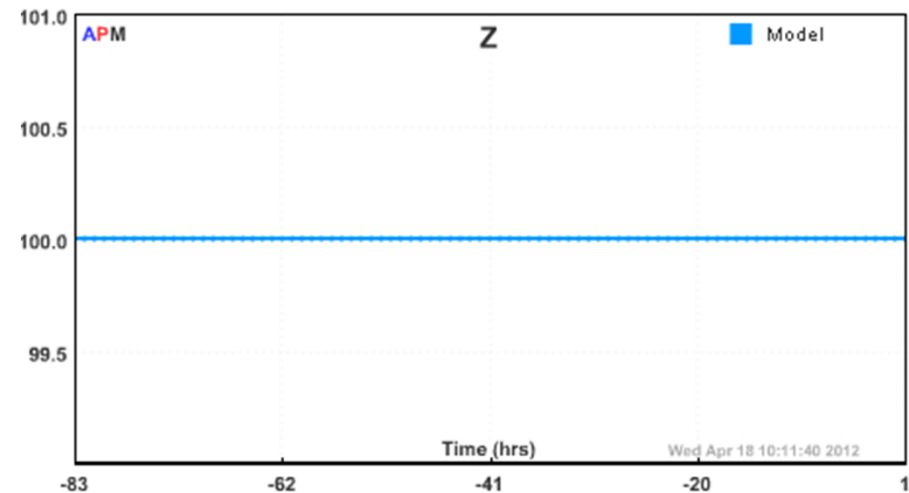
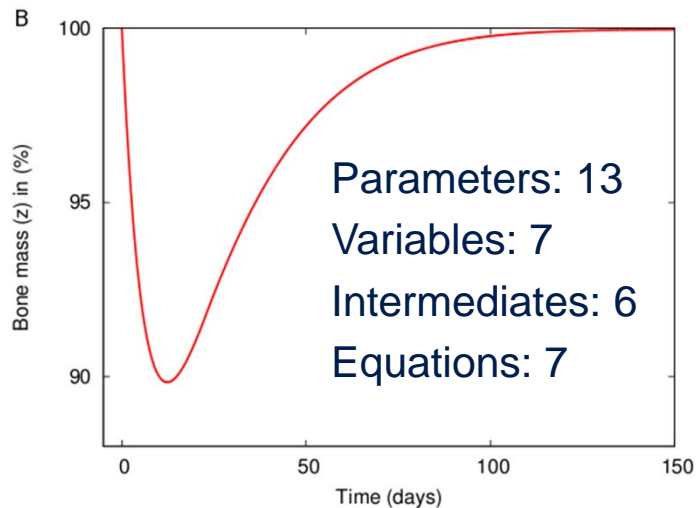
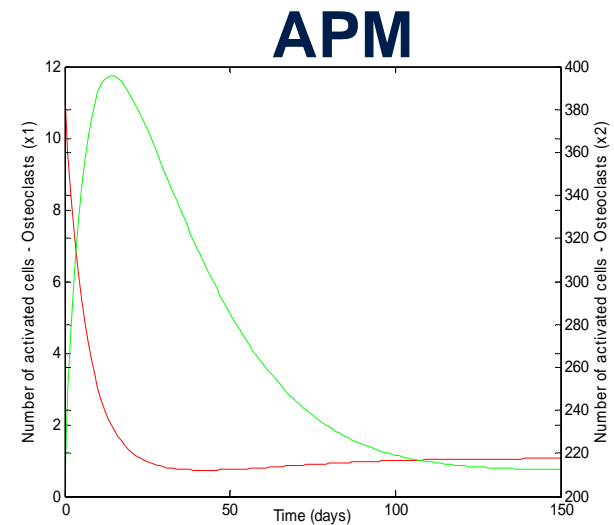
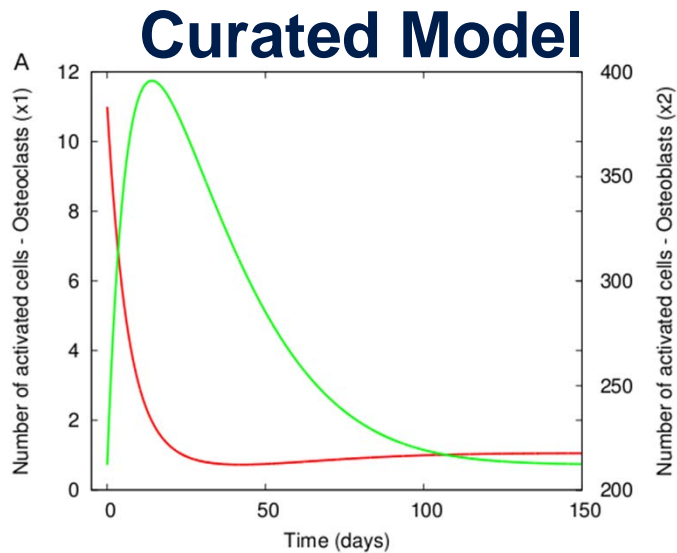


## APM



Parameters: 24  
Variables: 14  
Intermediates: 17  
Equations: 14

# Examples: Komarova2003\_BoneRemodeling



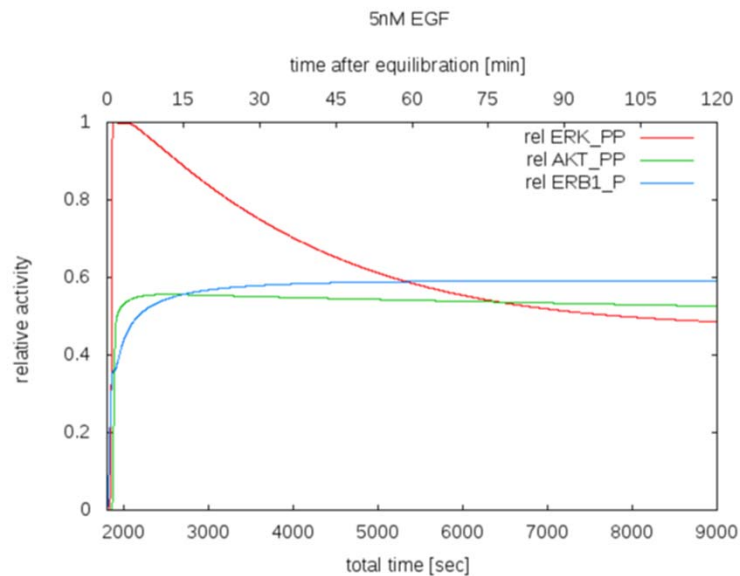
Converter does not automatically handle events or piecewise yet



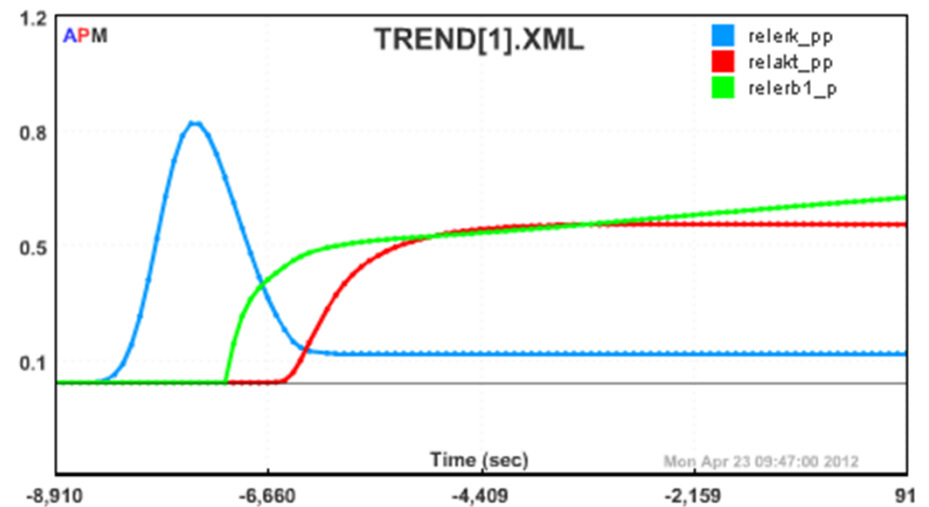
# Examples: Chen2009\_ErbB\_Signaling



## Curated Model



## APM



Parameters: 225

Variables: 504

Intermediates: 827

Equations: 504

# Computational Time in APM



	Variables	Time Steps	CPU Time (sec)	CPU/Time Step
Bone Remodeling <sup>1</sup>	11	150	1.40	0.0093
NFAT Activation <sup>1</sup>	30	100	2.19	0.0219
Vaccination Invasion <sup>1</sup>	37	100	3.06	0.0306
ErbB <sup>1</sup>	504	100	54.70	0.5470
ErbB <sup>2</sup>	504	100	22.70	0.2270



1 = Windows 7, Intel i7, 8 CPU  
7k RPM HD, gcc Compiler



2 = CentOS Linux, AMD, 64 CPU  
15k RPM HD, Intel Compiler

# Demo-How to use APM

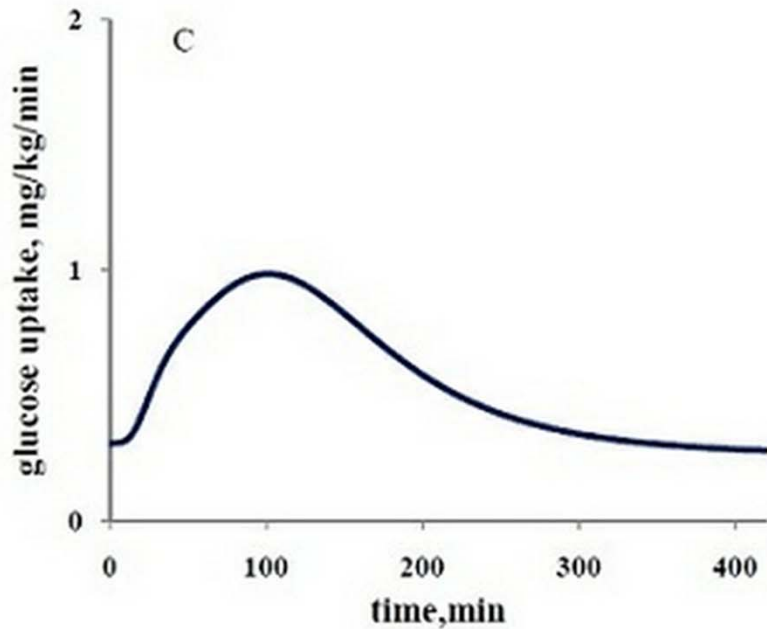


- **Simulate:**  
Nyman2011\_M3Hierararchical\_InsulinGlucosedynamics
- **Link to model:**
  - <http://www.ebi.ac.uk/biomodels-main/BIOMD0000000356>
- **Convert using APM version of SBML2APM:**
  - <http://apmonitor.com/wiki/index.php/Main/SBML>
- **Verify time horizon and plotted variables**
  - Use a .csv to generate time steps
- **Plot using web interface version of APM**
  - [http://apmonitor.com/online/view\\_pass.php](http://apmonitor.com/online/view_pass.php)

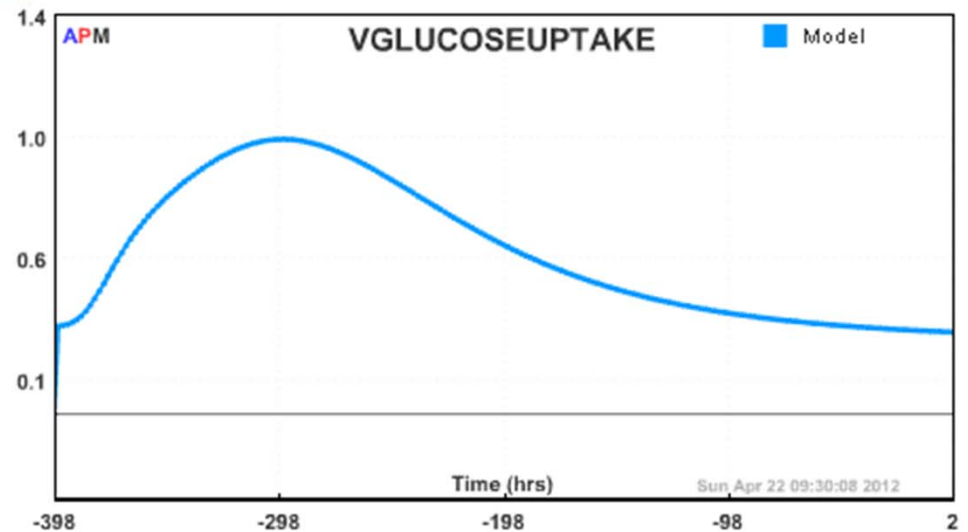
# Demo - Results



## Curated Model



## APM model



Parameters: 80

Variables: 67

Intermediates: 64

Equations: 67

# SBML2APM Future Development



- Piecewise models
- Event handling
- Addition of notes
- Auto-generated time steps
- Better unit display
- Benchmarking against the SBML Test Suite

# Using/Developing SBML2APM



- Convert SBML files to APM here:

- <http://apmonitor.com/wiki/index.php/Main/SBML>

- Open source for SBML2APM located at:

- <https://sbfc.svn.sourceforge.net/svnroot/sbfc/trunk/src/org/sbfc/converter>

# Getting Started with APM



- User group: [APMonitor@googlegroups.com](mailto:APMonitor@googlegroups.com)
- Join thousands of online users



# Conclusions



- Large Scale Biological Models can be solved with APM
- SBML2APM Converter tool
- Newly applied to Computational Biology
- Available in MATLAB, Python, or through a web interface



# Acknowledgements



- Vertex Collaboration
  - Large Scale Parameter Estimation
  - Identifying parameters to be estimated
- Casey Abbott
  - ErbB and HIV virus modeling applications
  - Parameter sensitivity studies
- Trevor Slade
  - MATLAB interfacing with APM/SBML
- Creators of the JSBML library and SBFC converter package
  - Andreas Dräger and Nico Rodriguez

# References

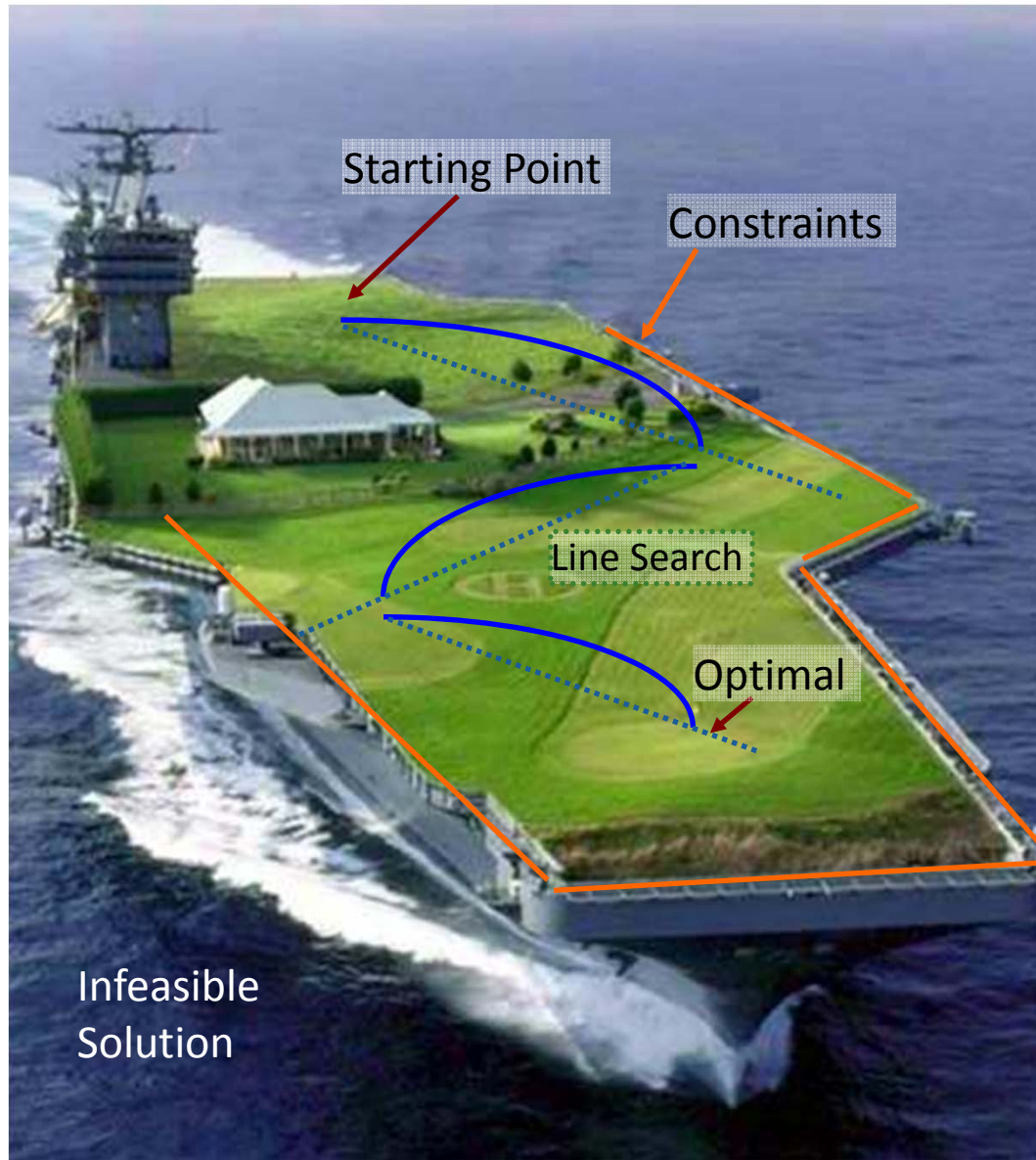


- Chen et al. [Mol Syst Biol.](#) 2009;5:239 .
- Dräger A, Rodriguez N, Dumousseau M, Dörr A, Wrzodek C, Le Novère N, Zell A, and Hucka M. **JSBML: a flexible Java library for working with SBML.** *Bioinformatics* (2011), 27(15):2167–2168.

# Additional Slides



# Navigate to an Optimal Solution



$$\min_{x \in \Omega} J(x, u)$$

$$s.t. \quad 0 = f(\dot{x}, x, u)$$

$$0 = g(x, u)$$

$$h(x, u) \geq 0$$

## Characteristics

Nonlinear

Multiple local minima

Mixed Integer

Large-scale

## Methods

Interior Point

Active Set

Global Search

Parallel Computation

Branch and Bound

# Survey of DAE Solvers

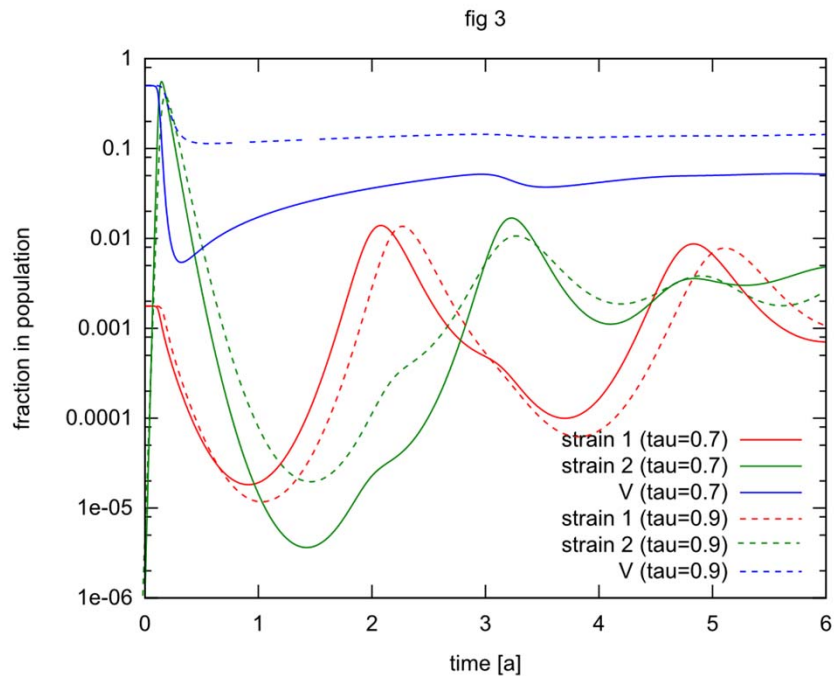


<u>Software Package</u>	<u>Max DAE Index</u>	<u>Form</u>	<u>Adaptive Time Step</u>	<u>Sparse</u>	<u>Partial-DAEs</u>	<u>Simultaneous Estimation / Optimization</u>
APMonitor	3+	Open	No	Yes	No	Yes
DASPK / CVODE	2	Open	Yes	No	No	No
gProms	1 (3+ with transformations)	Open	Yes	Yes	Yes	No
MATLAB	1	Semi-explicit	Yes	No	No	No
Modelica	1	Open	Yes	Yes	No	No

# Demo - Restif2007\_Vaccination\_Invasion



## Curated Model



Parameters: 12

Variables: 23

Intermediates: 26

Equations: 23

## APM

Differences in initial conditions

