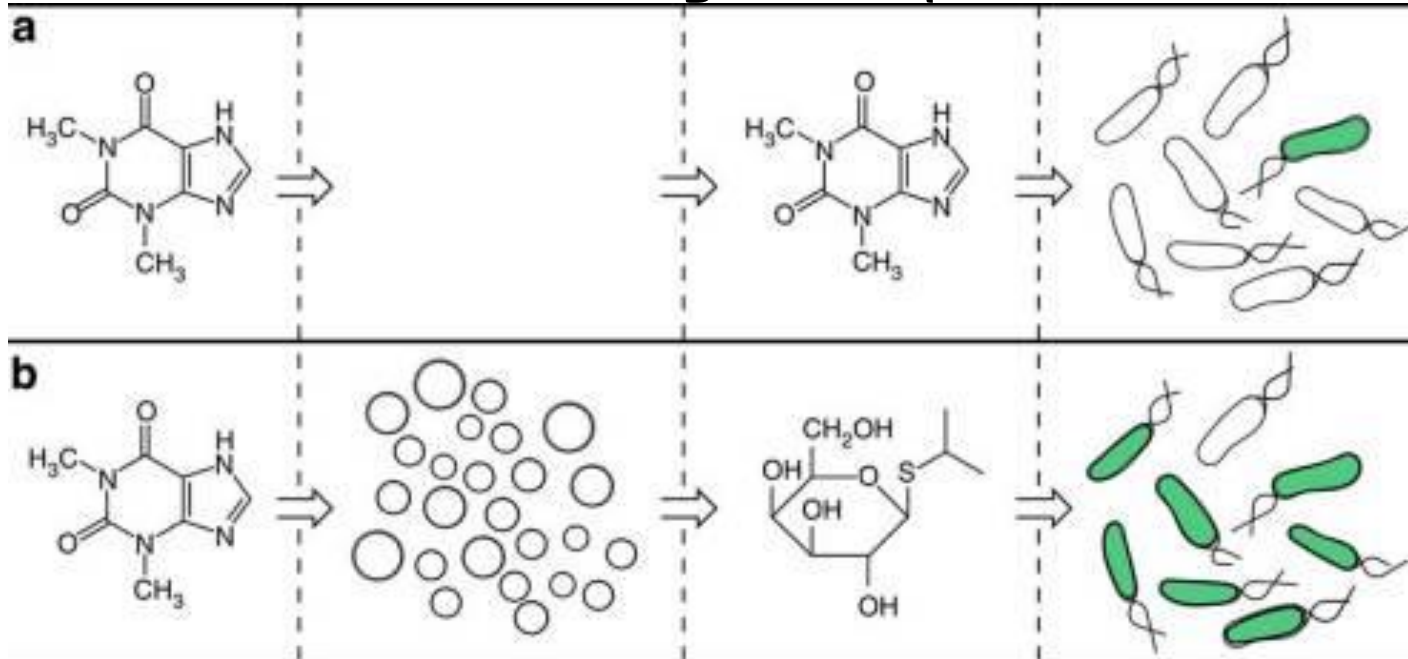


Sub-SBML: A Subsystem Interaction Modeling Python Toolbox for SBML Models

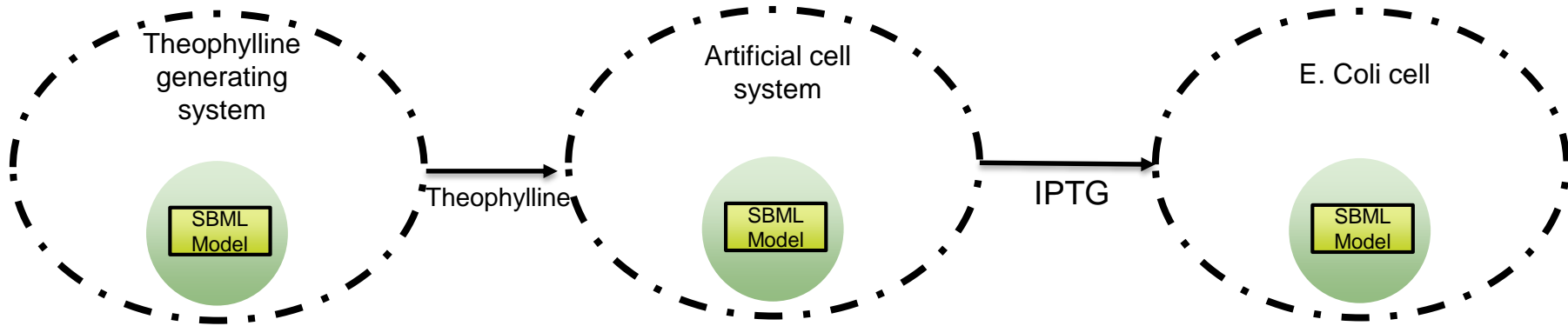
Ayush Pandey
Murray Lab, Caltech

A demonstrative modeling example



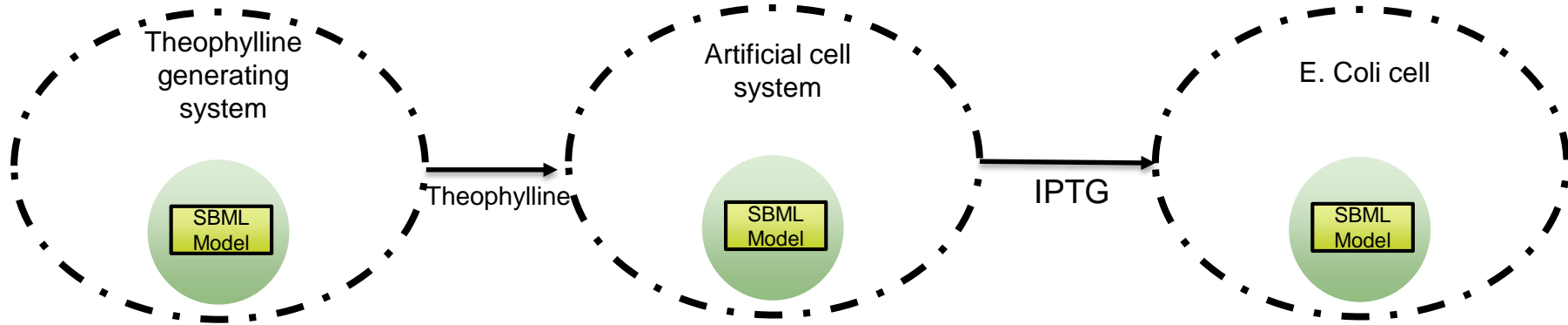
Reference : "Integrating artificial with natural cells to translate chemical messages that direct *E. coli* behavior", Roberta Lentini, Silvia Perez Santero et al. In: *Nature Communications*, 2014

How to model this system?



Reference : "Integrating artificial with natural cells to translate chemical messages that direct *E. coli* behavior", Roberta Lentini, Silvia Perez Santero et al. In: *Nature Communications*, 2014

How to model this system?



Create SBML model

Model transport/membranes
Create SBML model
Edit/Make compatible

Fetch SBML model
Model other interactions
Return combined model

Using existing tools – COPASI, iBioSim

COPASI 4.5 (Build 30) - Concentrations

Status	Name	Compartment	Type	Initial Concentration (mol/l)	Concentration (mol/l)	Rate (mol/l)
1	new species	C_1	reactions		1	
2		C_1	reactions		1	

Left sidebar menu: Copasi, Model, Biochemical, Compartments (C_1, C_2, C_3), Species, Reactions, Global Quantities, Parameter Overview, Mathematical Diagrams, Tasks, Output, Functions.

Buttons at the bottom: Commit, Revert, Clear, Delete/Undelete, New.

LacI_Inverter.xml* | Species Editor

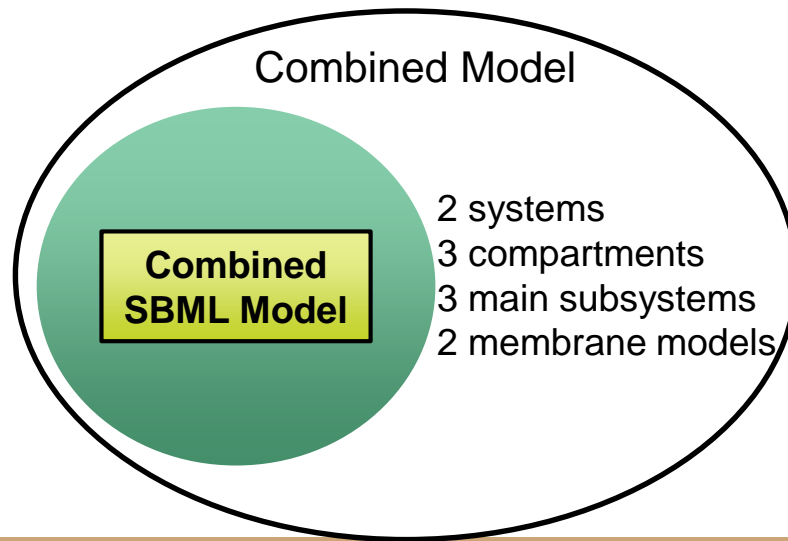
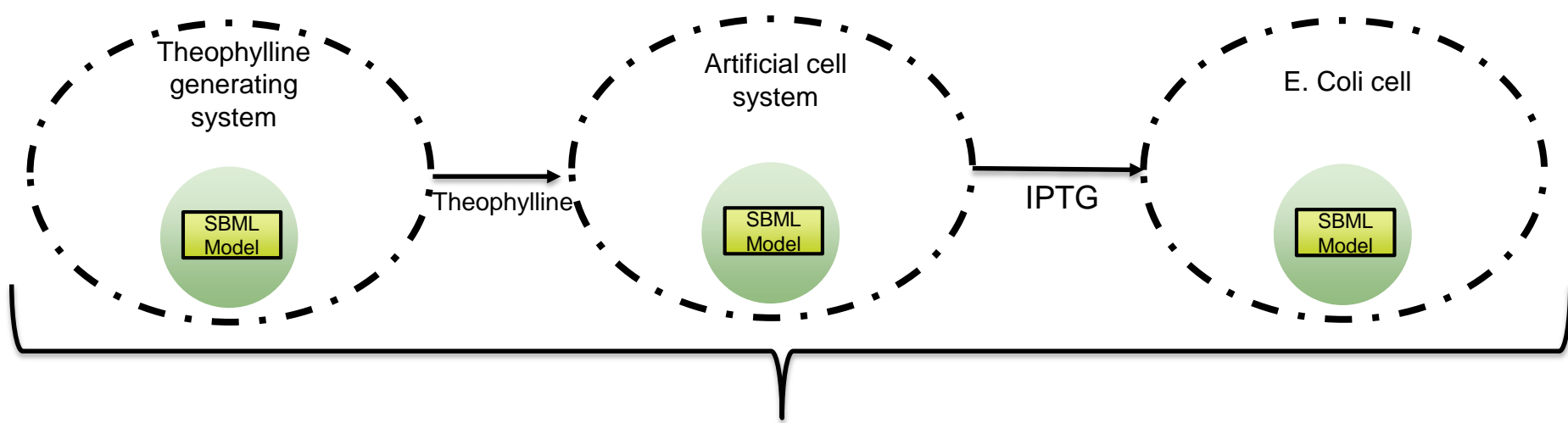
Diagram: A box labeled 'S0 internal' with four green handles.

Species Editor fields:

- ID: LacI
- Name: [empty]
- Port Type: input
- Compartment: Cell
- Compartment Indices: [empty]
- Initial Amount/Concentration: 0.0
- Units: (none)
- Conversion Factor: (none)
- Conversion Factor Indices: [empty]
- Boundary Condition
- Constant
- Has Only Substance Units
- Constitutive
- Degrades
- Diffusible
- Open complex production rate (ko): default | 0.05
- Stoichiometry of production (np): default | 10.0
- Degradation rate (kd): default | .0075
- Complex formation equilibrium (Kc): default | 0.05/1
- Membrane diffusion rate (fd/rv) (kmdiff): default | 1.0/0.01
- SBOL DNA Component: Associate SBOL

Buttons: Cancel, Ok.

Using Sub-SBML...

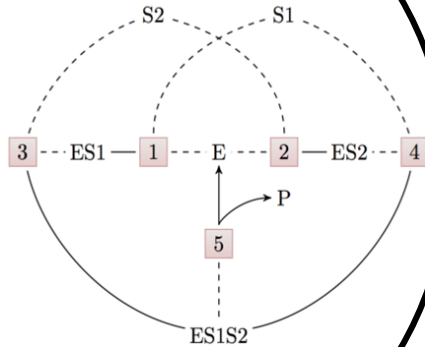




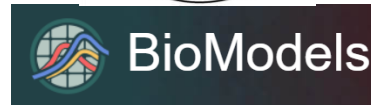
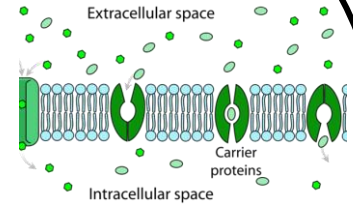
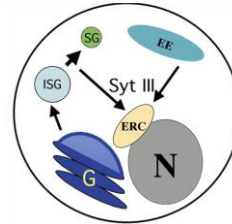
TX-TL



in vivo



Create Models



Compile Models

Model Reduction

Analysis with Models

Sensitivity analysis

System identification

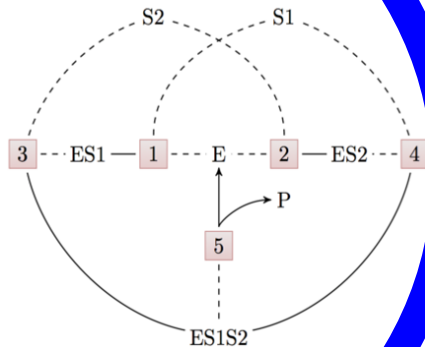
Guiding experiments

SBML.org

TX-TL



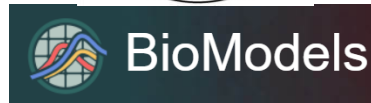
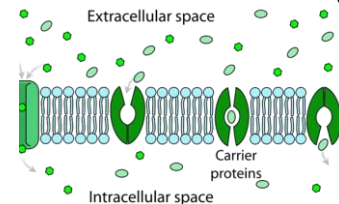
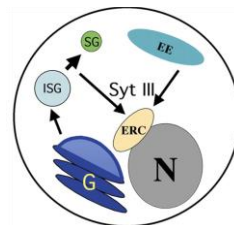
in vivo



Create Models

SBML

libSBML



Compile Models

Model Reduction

Analysis with Models

Sensitivity analysis

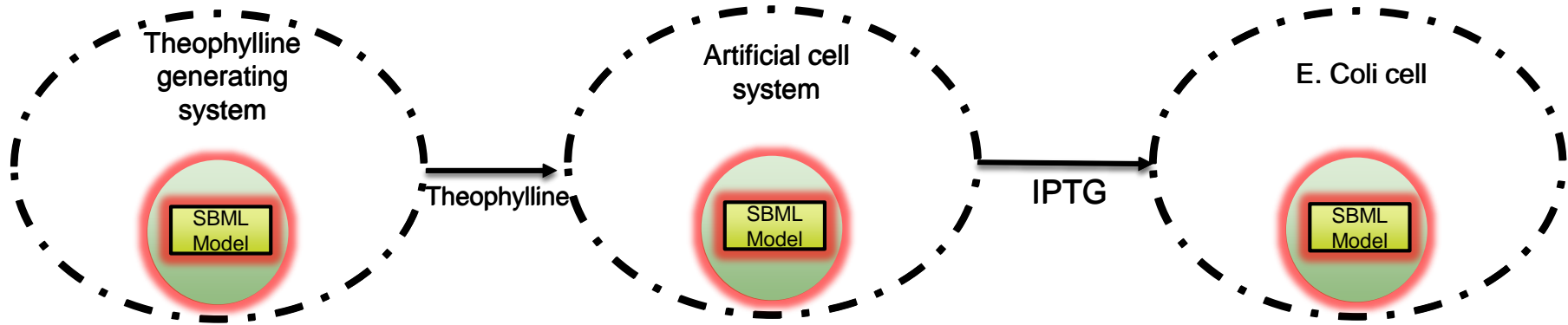
System identification

Guiding experiments

Create Models

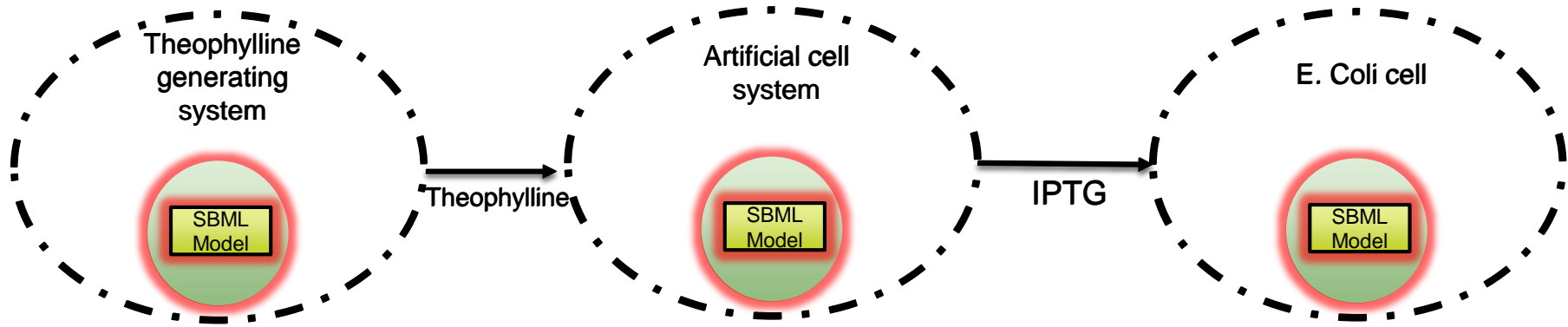
- Creating SBML models
 - Use Sub-SBML
 - ... or any other existing tool

Create SBML Subsystems



1. Create a new Subsystem
2. Load SBML file into subsystem / Create SBML components from scratch
3. Use libsbml API directly or simple commands in subsbml

Create SBML Subsystems



```
artificial_cell = createNewSubsystem(), model = artificial_cell.getModel()  
model.createNewSpecies(ListOfSpecies, ListofAmounts, ... ) ...
```

OR

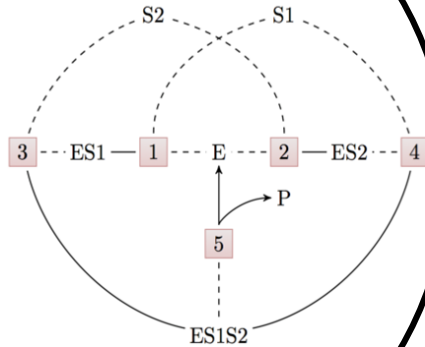
```
artificial_cell = createSubsystem('load_model.xml')
```



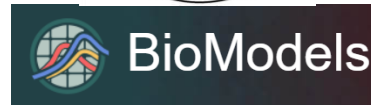
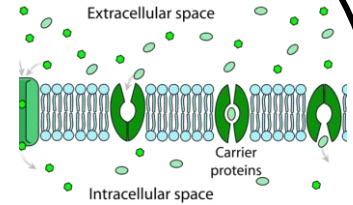
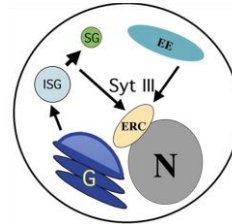
TX-TL



in vivo



Create Models



Compile Models

Model Reduction

Analysis with Models

Sensitivity analysis

System identification

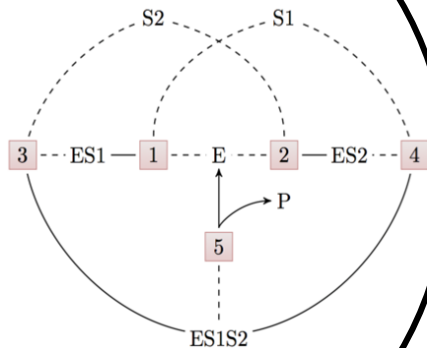
Guiding experiments

SBML.org

TX-TL

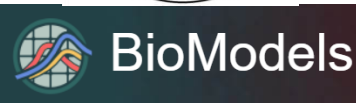
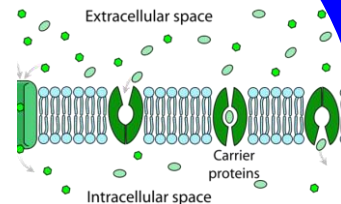
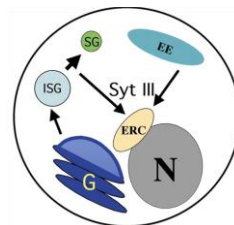


in vivo



Create Models

SBML libSBML



Compile Models

Model Reduction

Analysis with Models

Sensitivity analysis

System identification

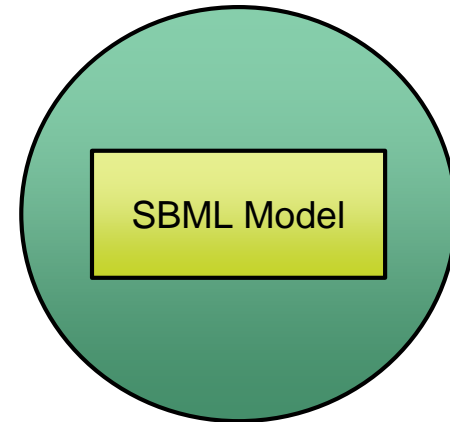
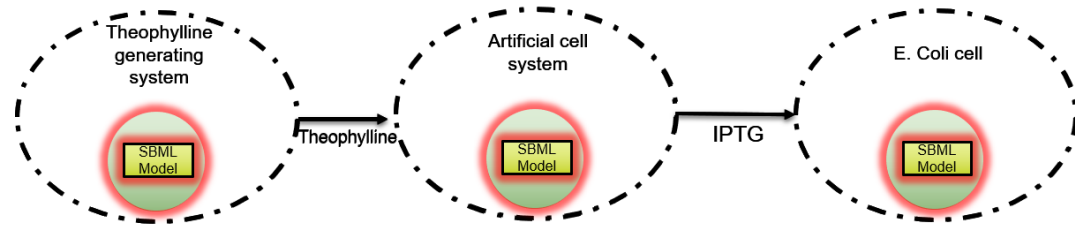
Guiding experiments

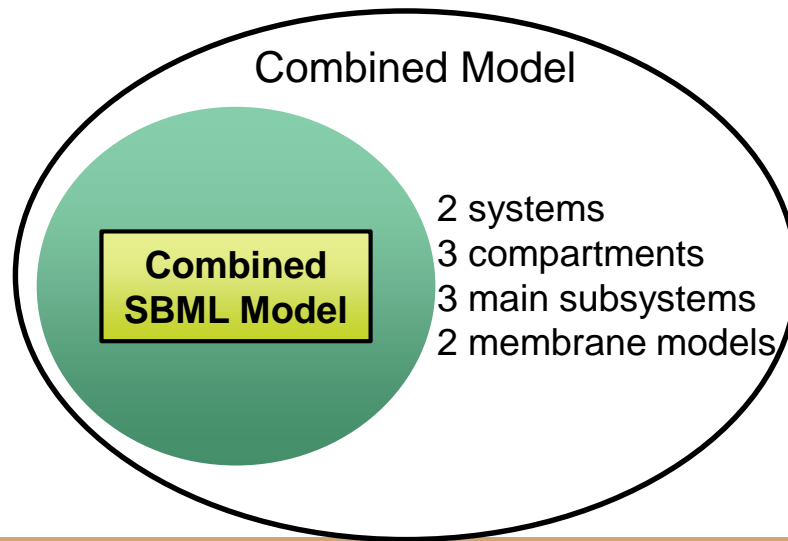
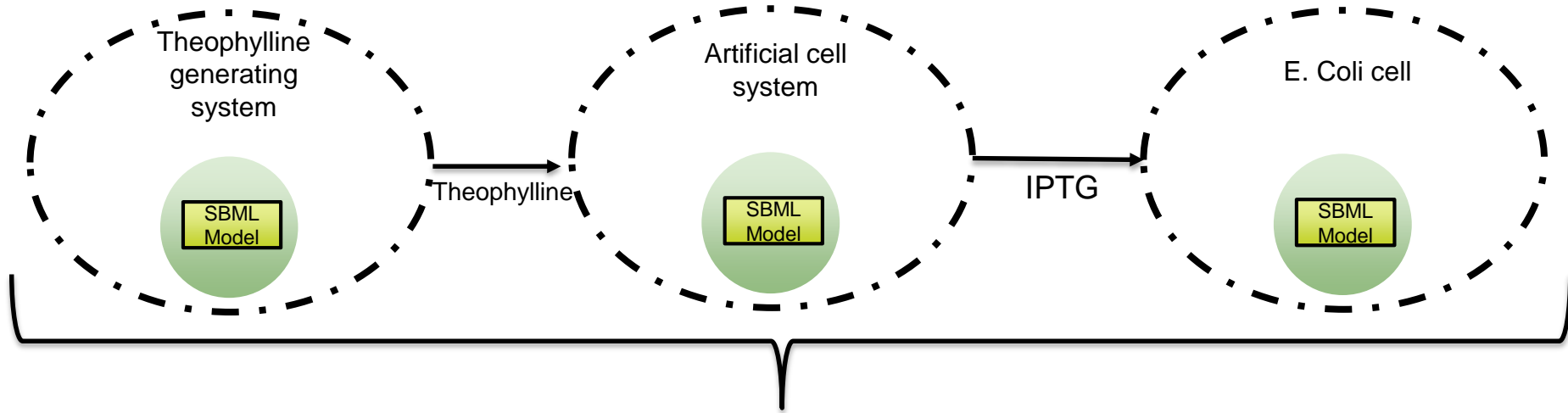
Compile Models

- Utility of Subsystems
- Combining multiple SBML models
- Transport and compartment modeling
 - Interactions between different compartments
 - Modeling of transport across membranes

Modeling Subsystems

- Contains one SBML model
 - 1 compartment model
- Various utility functions available for Subsystems to edit models
 - Compiling multiple models
 - Interaction modeling
 - Simulating variable inputs
 - Analysis tools
- Other applications can be built on top of Subsystem architecture of modeling





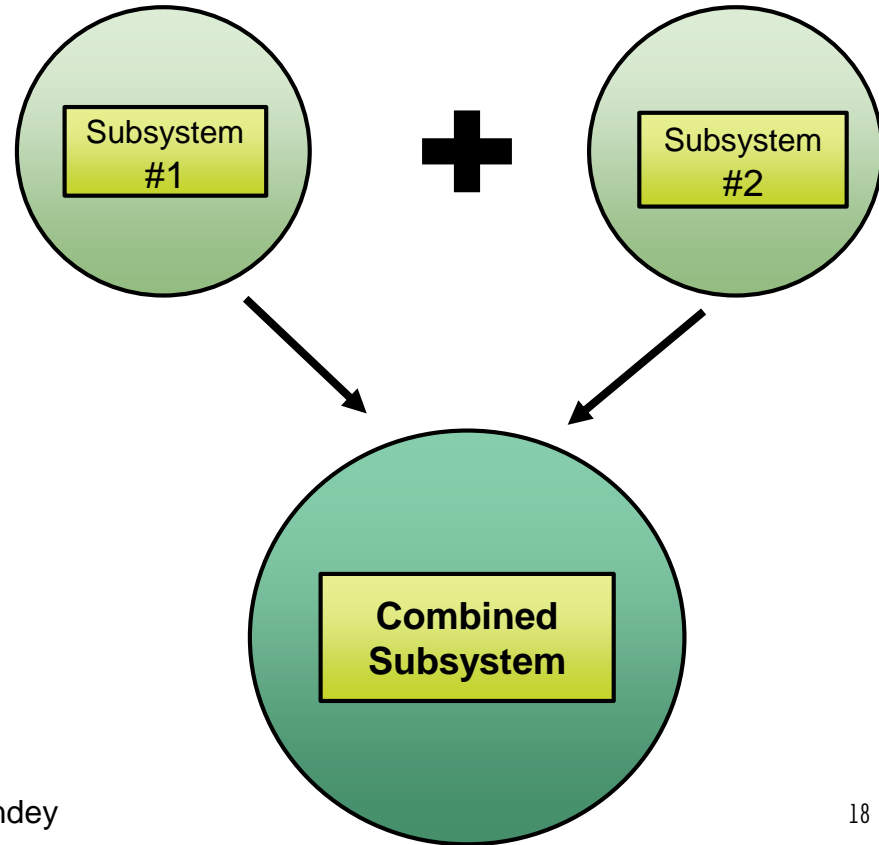
Combining Subsystems

- What about common components?
- Shared resources?
- Duplicate species?
- Duplicate reactions?
- Other interactions?

Sub-SBML provides

- *shareSubsystems*
- *combineSubsystems*
- *connectSubsystems*

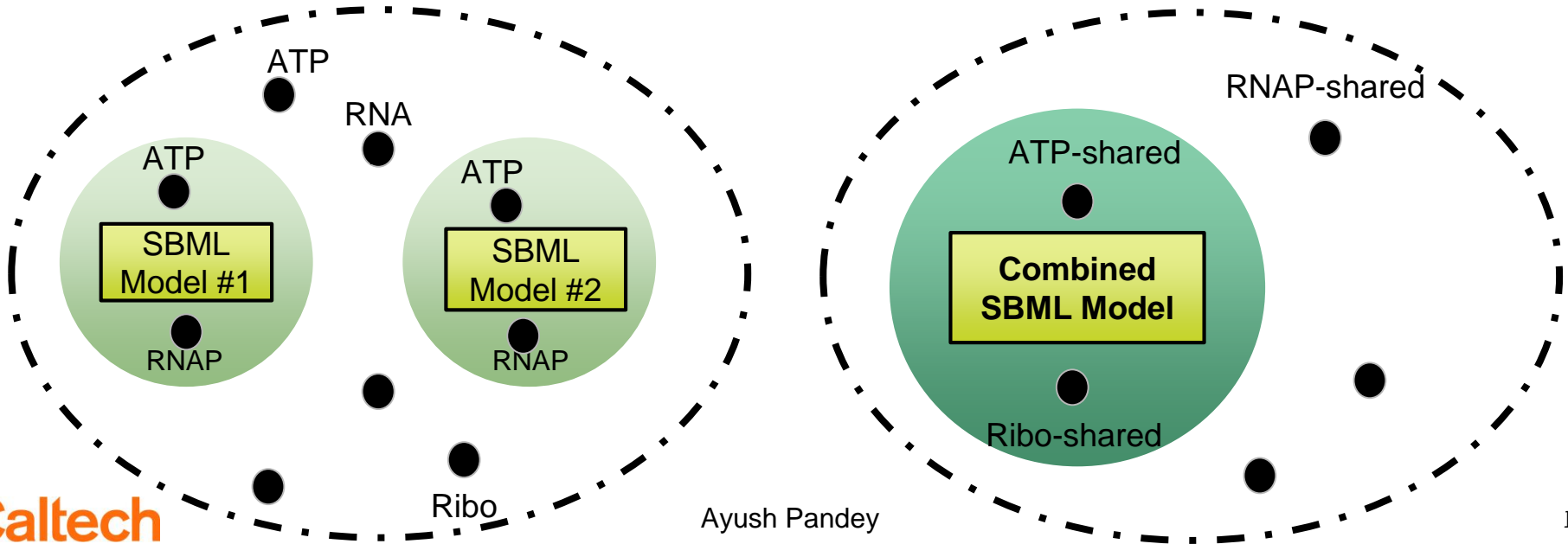
And builds other tools using these....



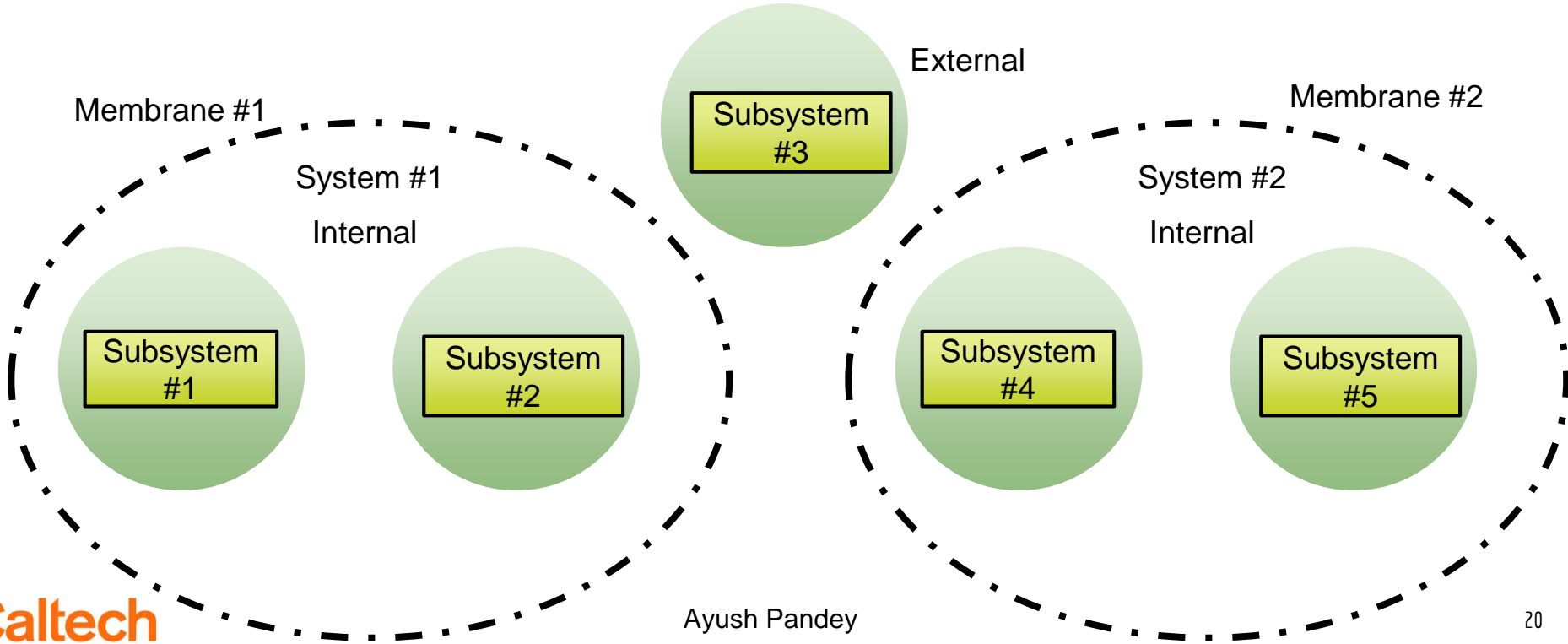
Modeling : Shared Resources

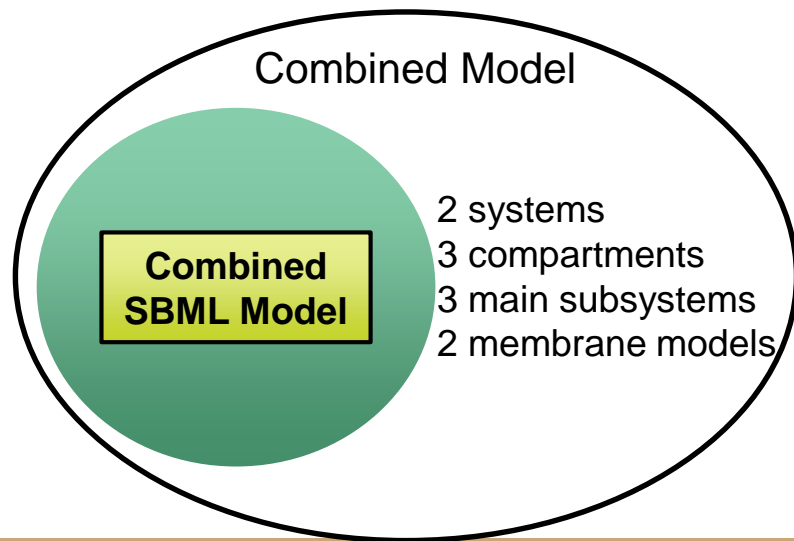
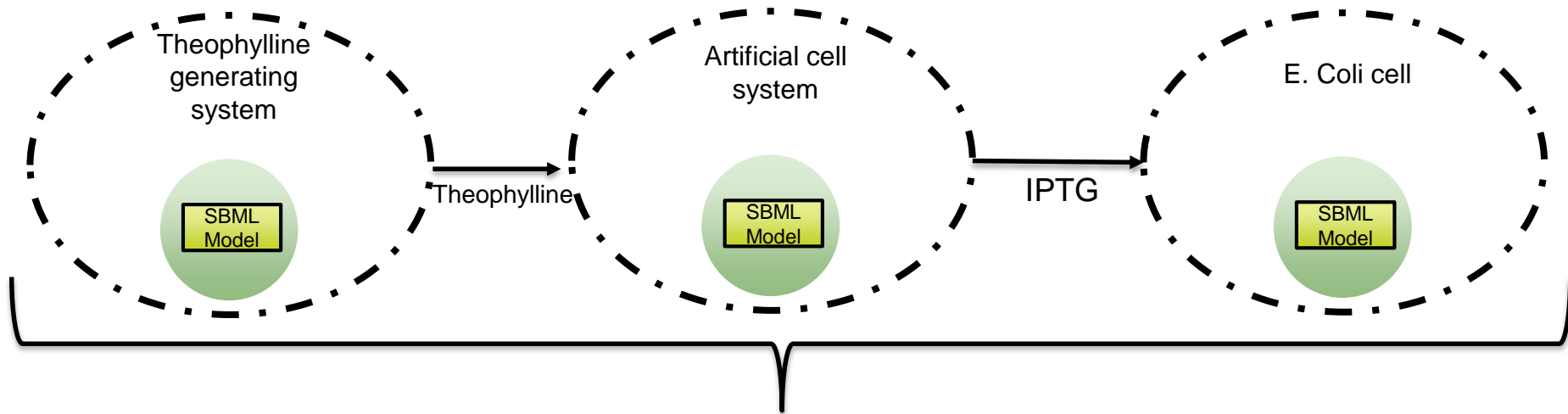
Usage -

```
cell = System()  
cell.createSubsystem('SS1.xml'), cell.createSubsystem('SS2.xml')  
shared_model = cell.setSharedResources(['ATP', 'RNAP', 'Ribo'])
```

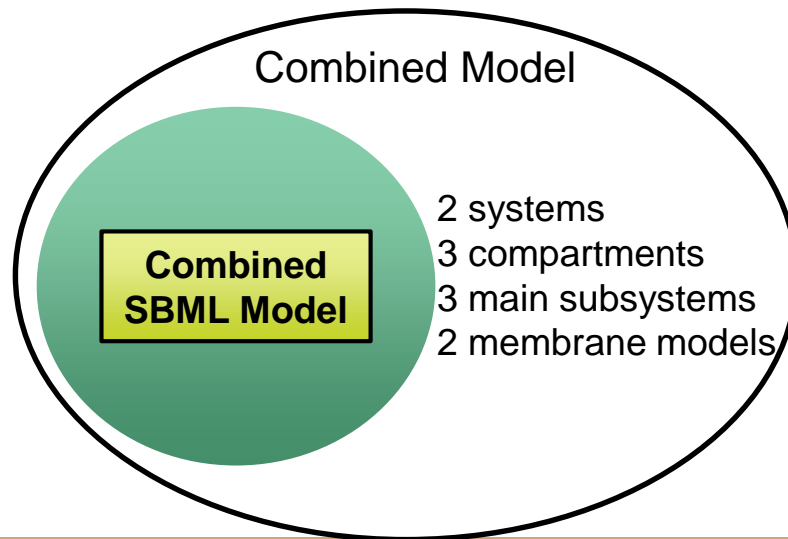
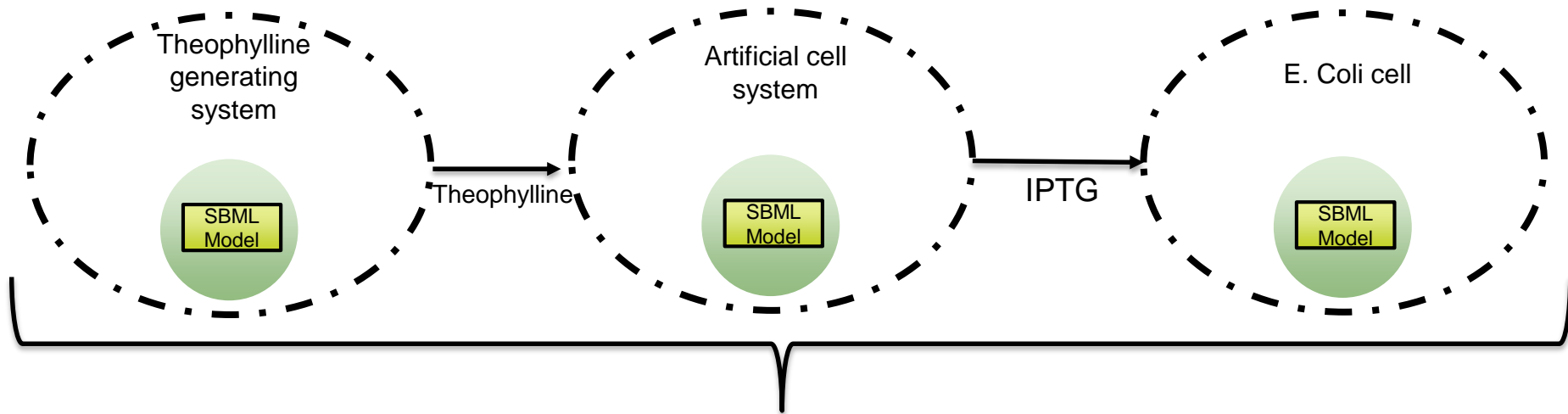


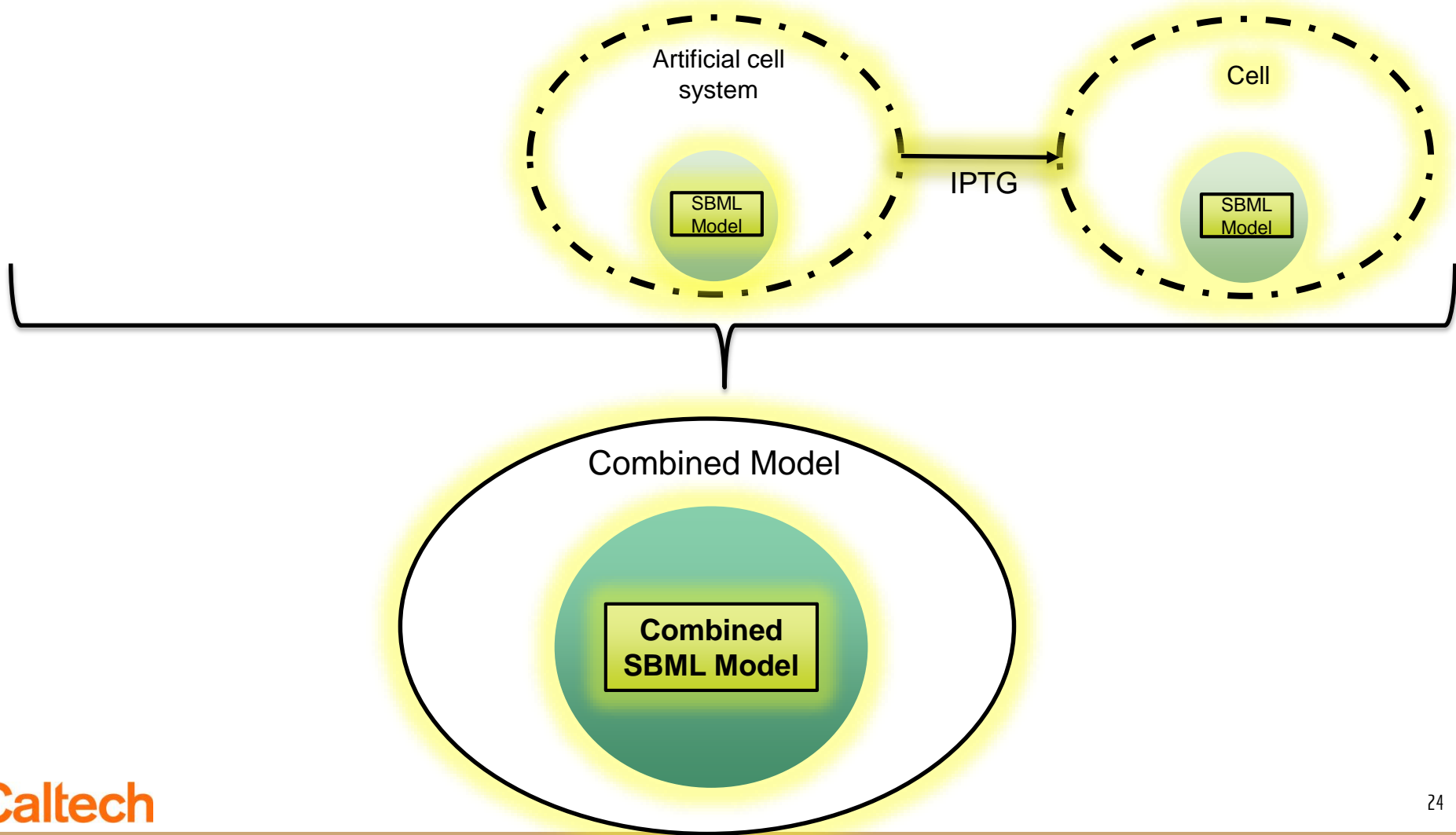
“Subsystems” inside a “System”

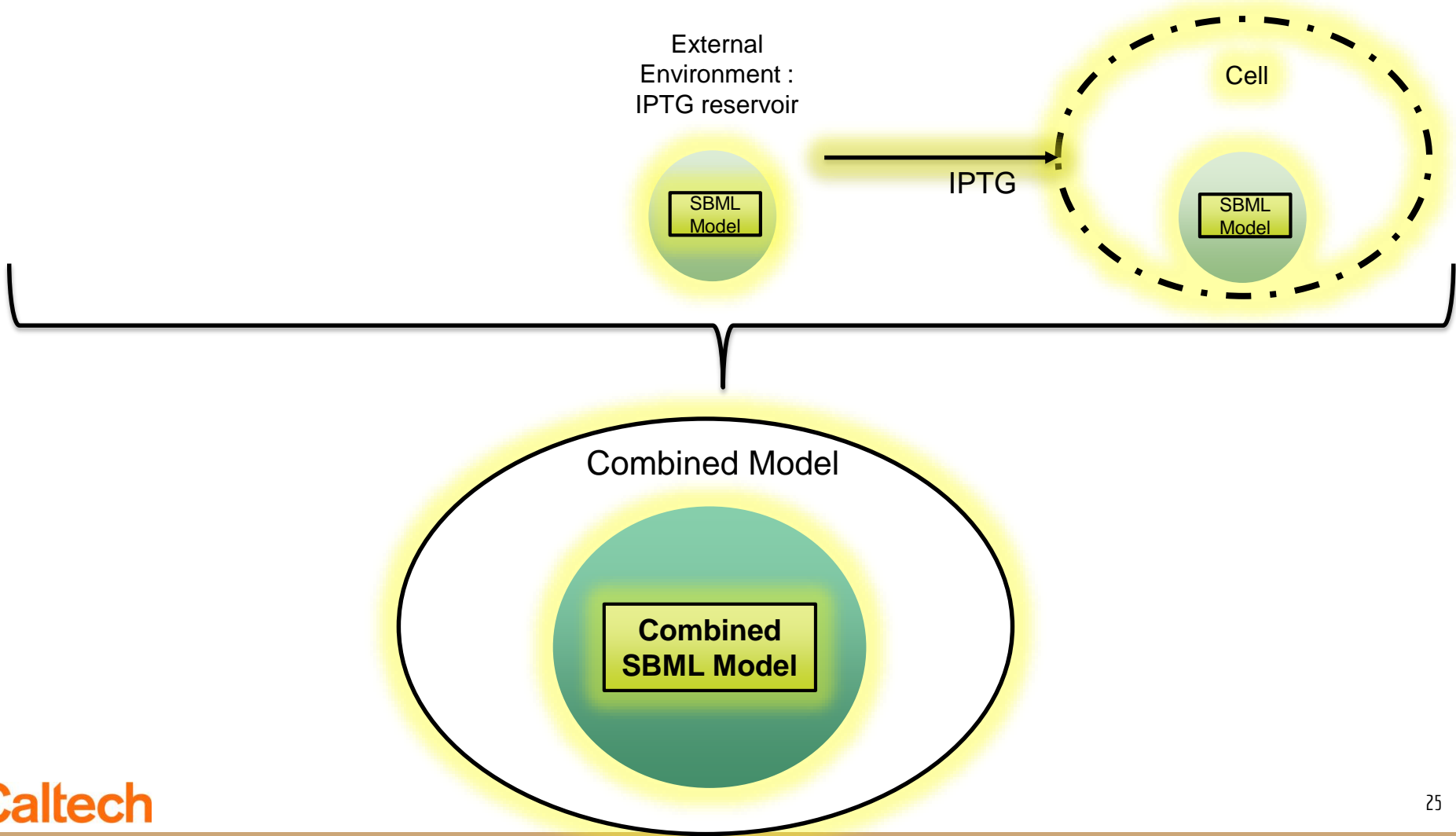




Considering only IPTG
transport module...

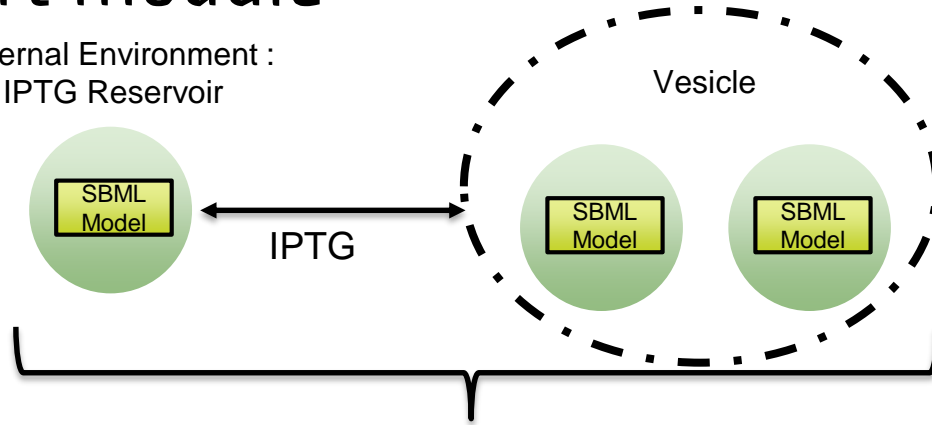




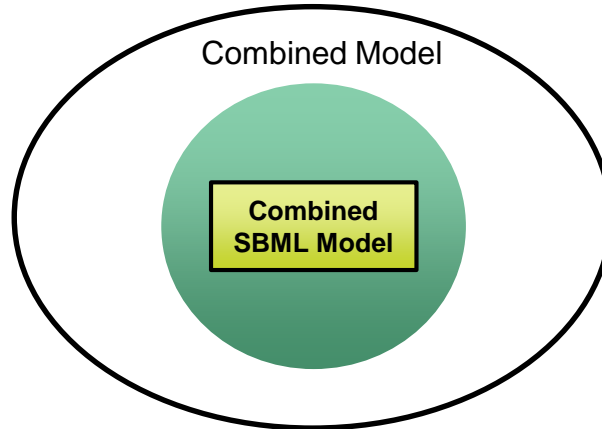


IPTG transport module

External Environment :
IPTG Reservoir



Combined Model



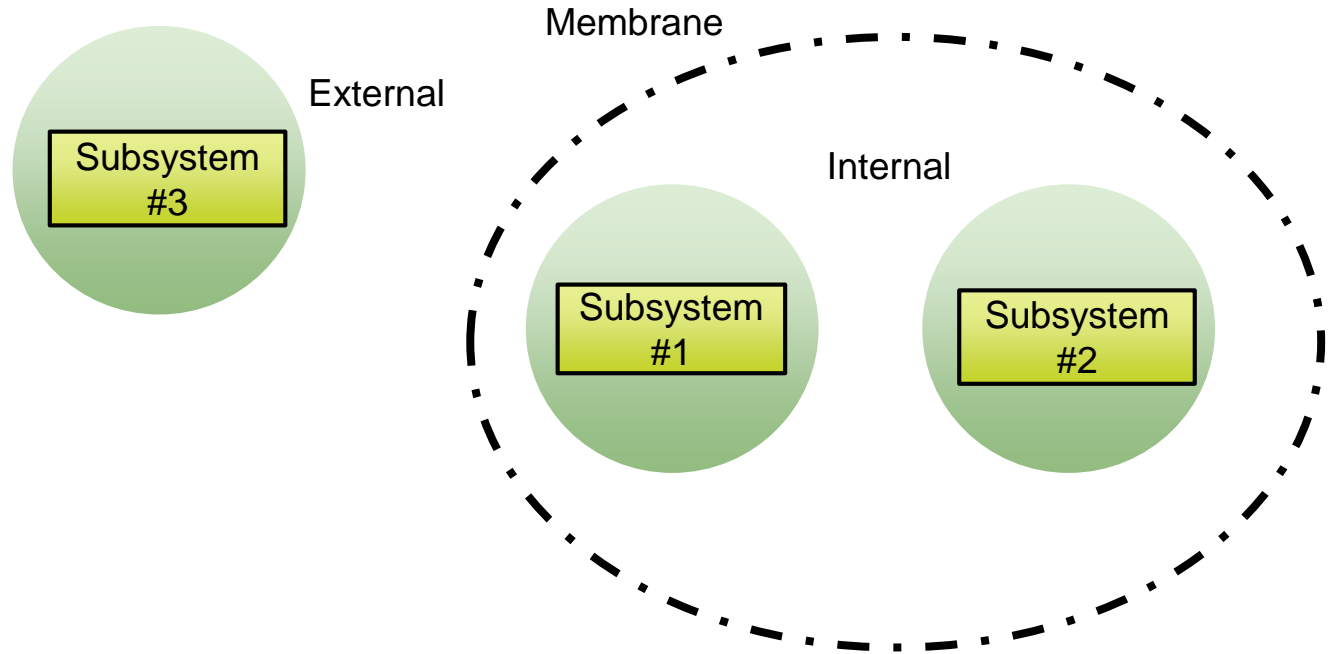
IPTG Transport Modeling

Subsystem 1 -
pOR1OR2-alpha-
Hemolysin

Subsystem 2 -
pLac-deGFP
pOR1OR2-LacI

External -
IPTG reservoir

Membrane -
Allows IPTG
transport

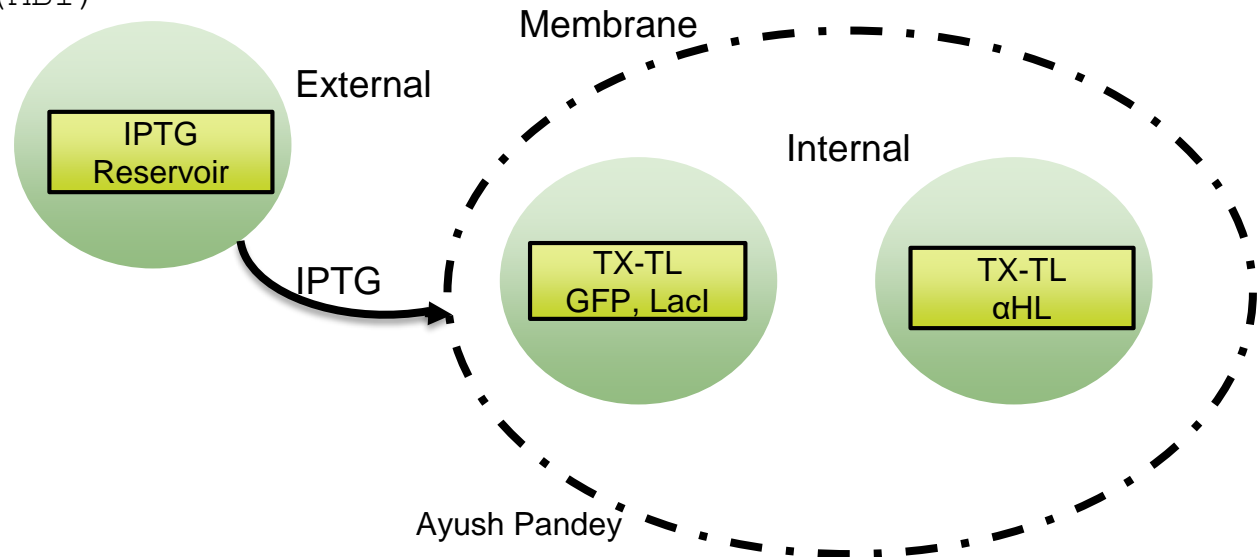


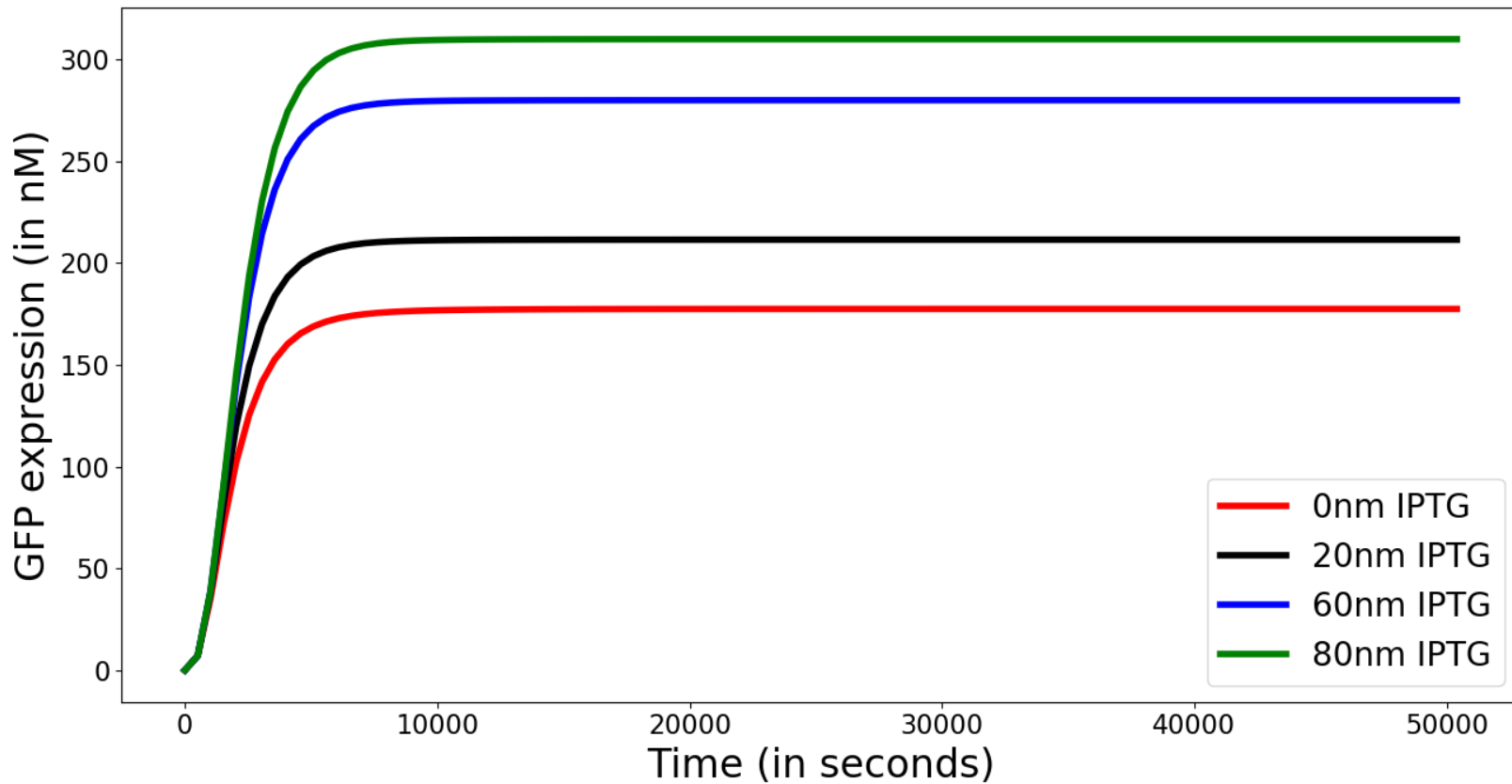
Modeling using Sub-SBML

Modeling -

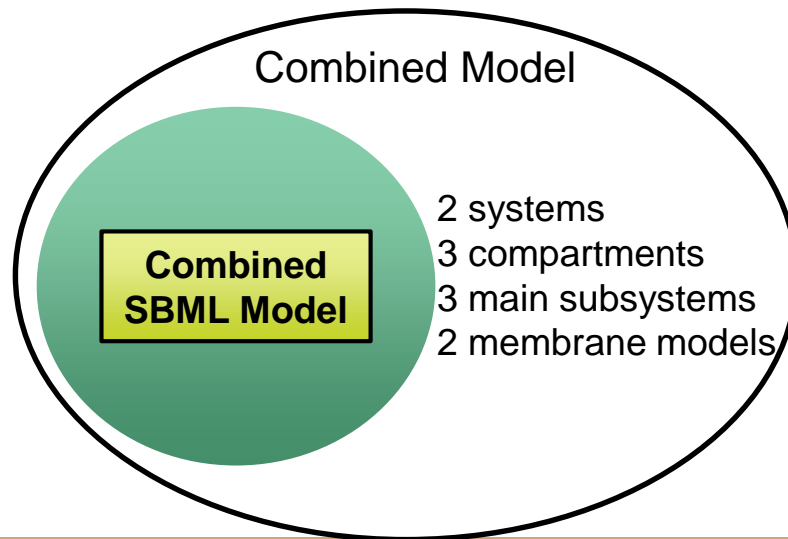
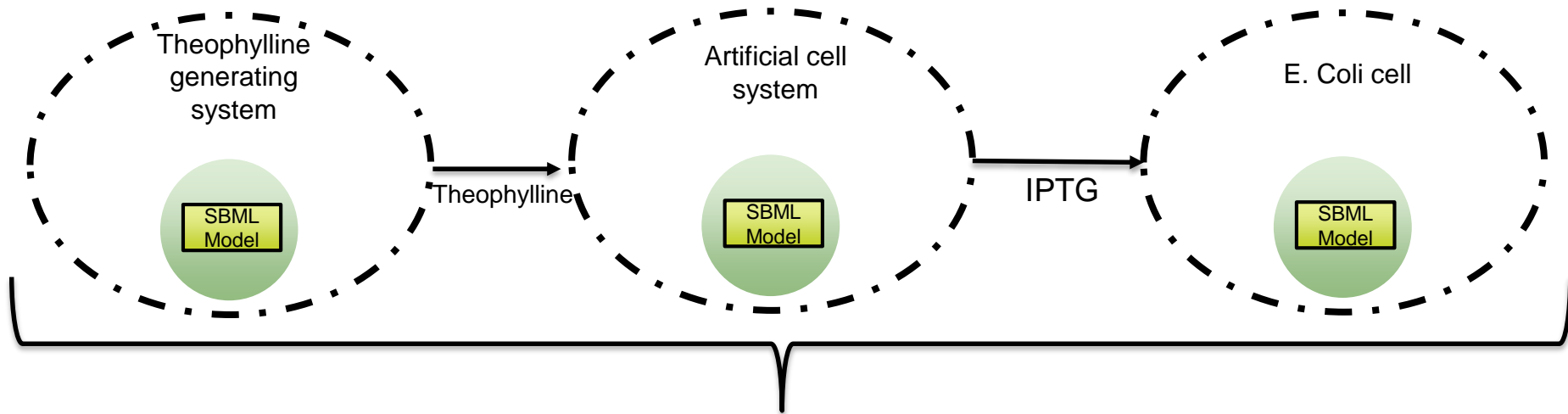
```
sys1 = System(),  
SS1 = sys1.createSubsystem('SS1.xml'), ...and so on  
sys1.setInternal([SS1, SS2])  
sys1.setExternal(SS3)  
sys1.setMembrane(MB1)
```

```
model = sys1.getModel()
```





Now including all other
modules...



Code in Sub-SBML

```
ss1 = createSubsystem('theophylline.xml')
ss2 = createSubsystem('artificial_cell.xml')
ss3 = createSubsystem('e_coli.xml')

mb1 = createSubsystem('membrane_artificial.xml')
mb2 = createSubsystem('membrane_IPTG.xml')

sys1 = System('cell1', [ss1,ss2], mb1)
sys2 = System('cell2', ss3, mb2)

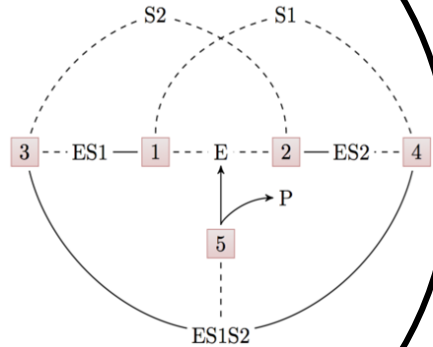
combined_model = combineSystems(sys1.getModel(), sys2.getModel())
```



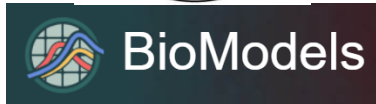
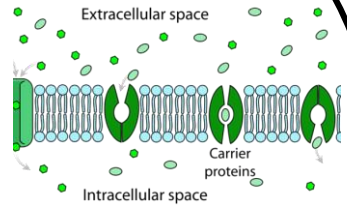
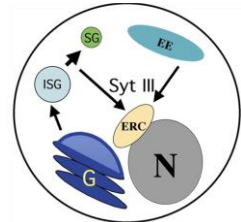

TX-TL



in vivo



Create Models



Compile Models

Model Reduction

Analysis with Models

Sensitivity analysis

System identification

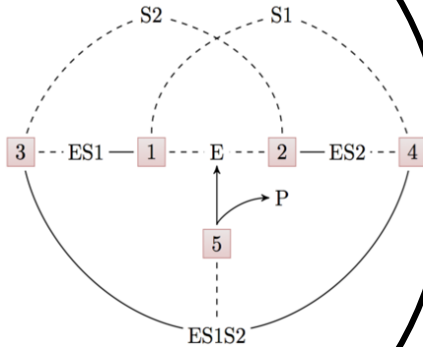
Guiding experiments

SBML.org

TX-TL

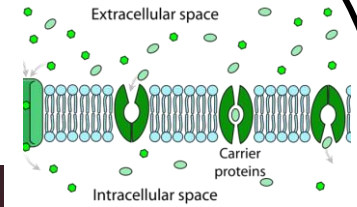
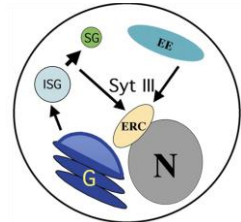


in vivo



Create Models

SBML libSBML



BioModels

Compile Models

Model Reduction

System identification

Analysis with Models

Sensitivity analysis

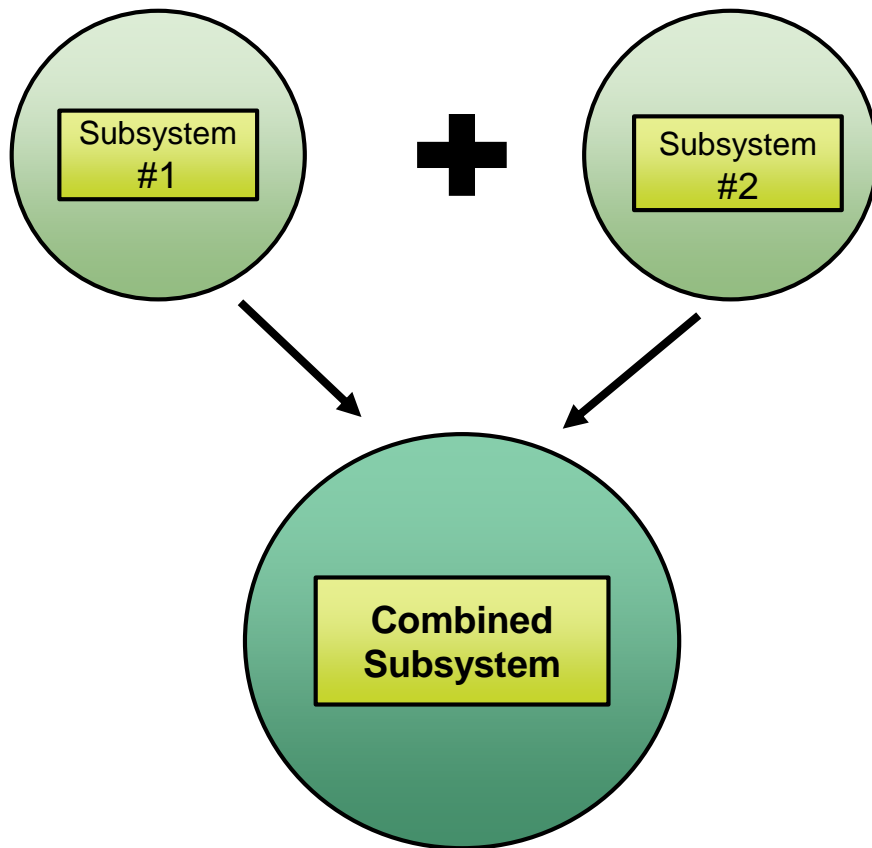
Guiding experiments

Summary



Takeaway #1

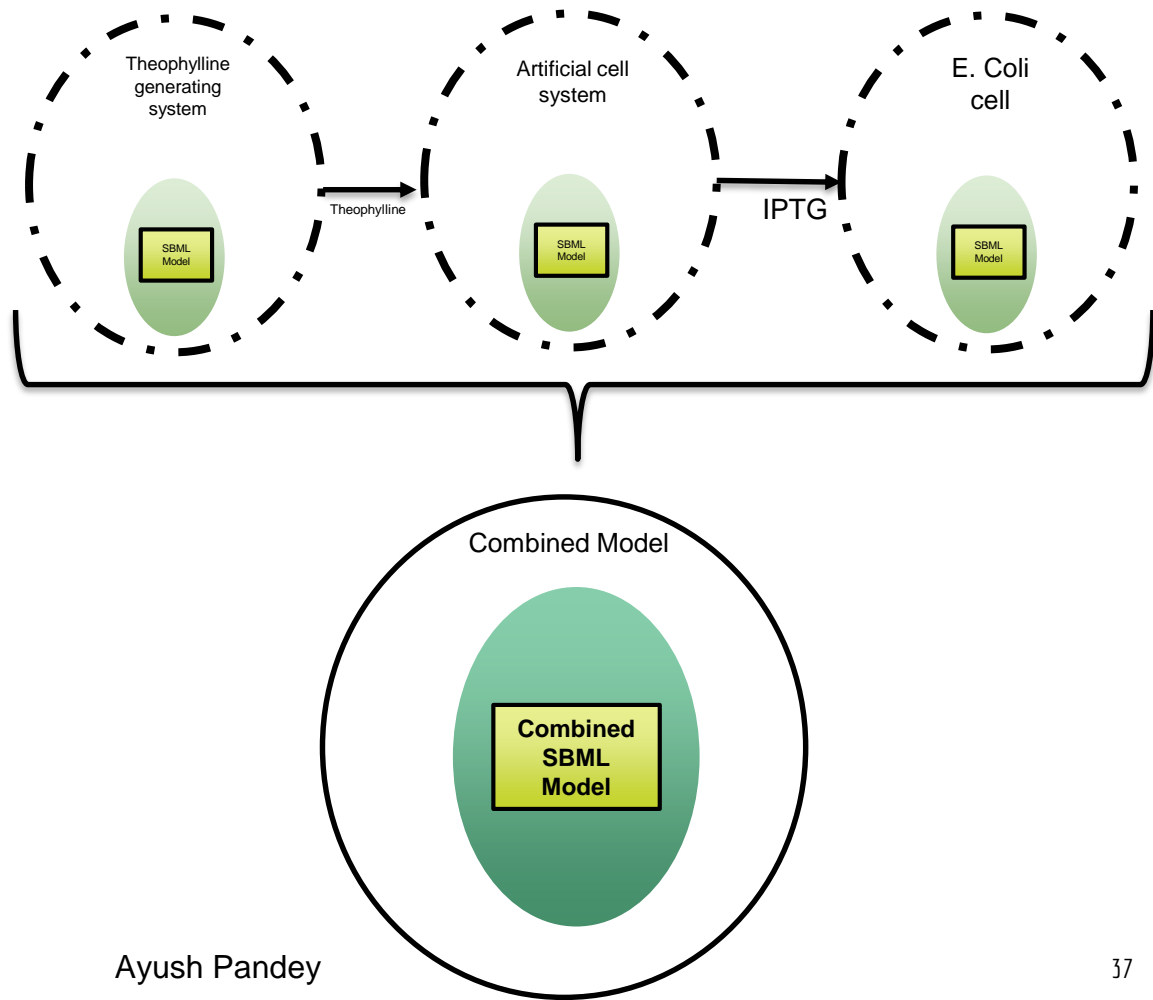
Helpful functions to model interactions between multiple SBML models developed using a “subsystem” framework



Takeaway #2

Structured, and simple modeling of transport across membranes and other interactions between systems.

Important tools for model reduction can be built on this framework.



Acknowledgments

Thanks to help and support from:

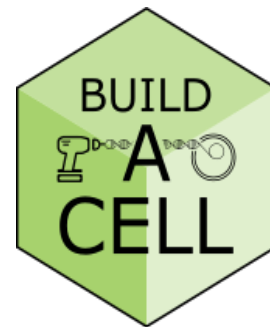
- Prof. Richard Murray



- Vipul Singhal, Anandh Swaminathan



- William Poole, Zoila Jurado



All code available and open source on –
Github -> BuildACell -> subsbml

<https://github.com/BuildACell/subsbml/>

Backup slides