System Level Development of a Platform for Studying Bacterial Biofilms

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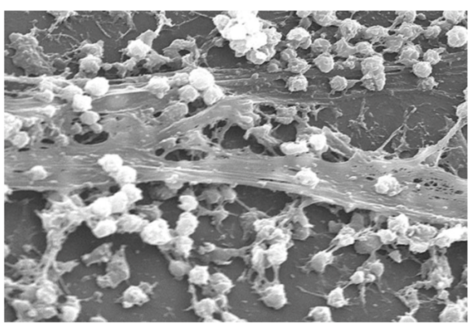
Motivation

- Bacterial Biofilms
  - Responsible for 65 – 80 % of all infections
  - 90% of harmful bacteria exist as biofilms at a point in their lifetime
  - Formation of biofilms initializes release of harmful toxins
  - Density of biofilms makes drug treatment more difficult
- Application Areas
  - Pharmaceutical development
  - Biological research
  - Environmental applications

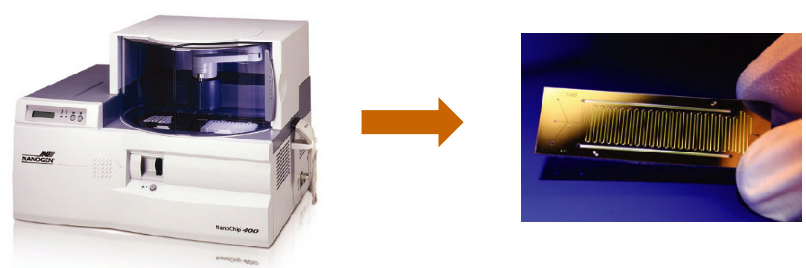
Motivation

Investigation of biofilms can be <u>expensive</u> and <u>time consuming</u>!

- Microfluidics
  - Drastically decreases fluid volumes (mL → μL)
  - Drastically decreases assay time (days → hours)
- Modeling
  - Overall decrease in the number of experiments needed
  - Overall increase in confidence in results



Bacterial Biofilm Found in a Catheter (www.cdc.gov)



Biomedical Testing Instrumentation (Nature: Methods)

Goals and Scenarios

- Integrated Experimental Platform
  - Microfluidic environment for biofilm growth
  - Computer-based model for biofilm growth simulation and parametric analysis
  - Integrated sensor network to detect growth *in situ*
  - Interfacing of hardware components and software
- Operation Scenarios
  - User-defined experiment parameters based on simulation results
  - Real-time adjustment of experiment parameters to “direct” biofilm growth characteristics
  - High parallelism and easy system reuse

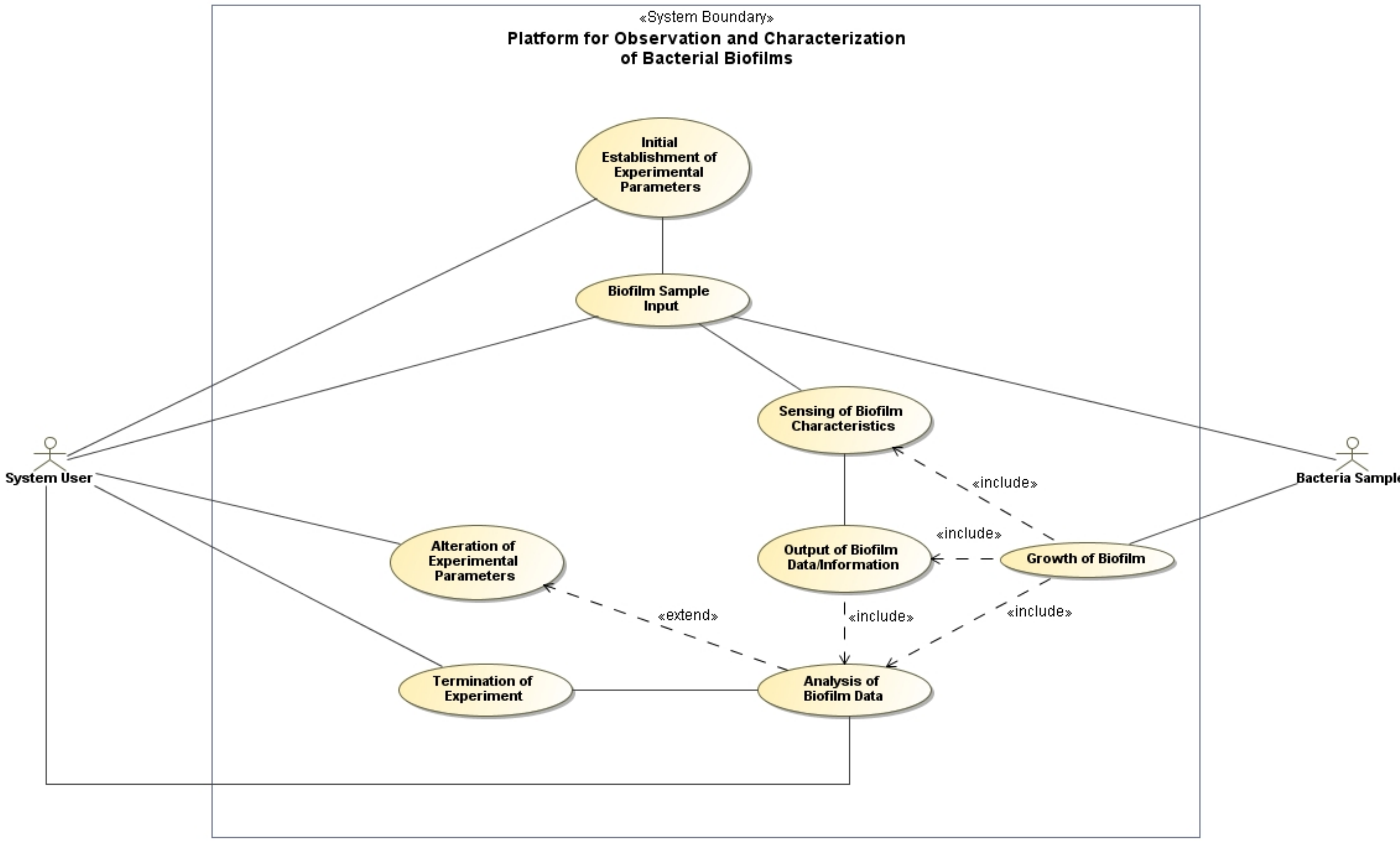
System-Level Requirements

Requirement Category	Req. Number	Description
Biofilm Growth Simulation	R1	Errors maintained within 10% of experimental results
Microfluidic Environment	R1	Repeatability of experiments within 20% variation
Sensing and Data Processing	R1	Self-contained system
	R2	Reliable with little internal error/variability
	R3	Non-invasive sensing method that can operate *in situ*
Experimental Control	R1	Real-time adjustment of experimental parameters
	R2	High user confidence in accuracy of experimental parameters

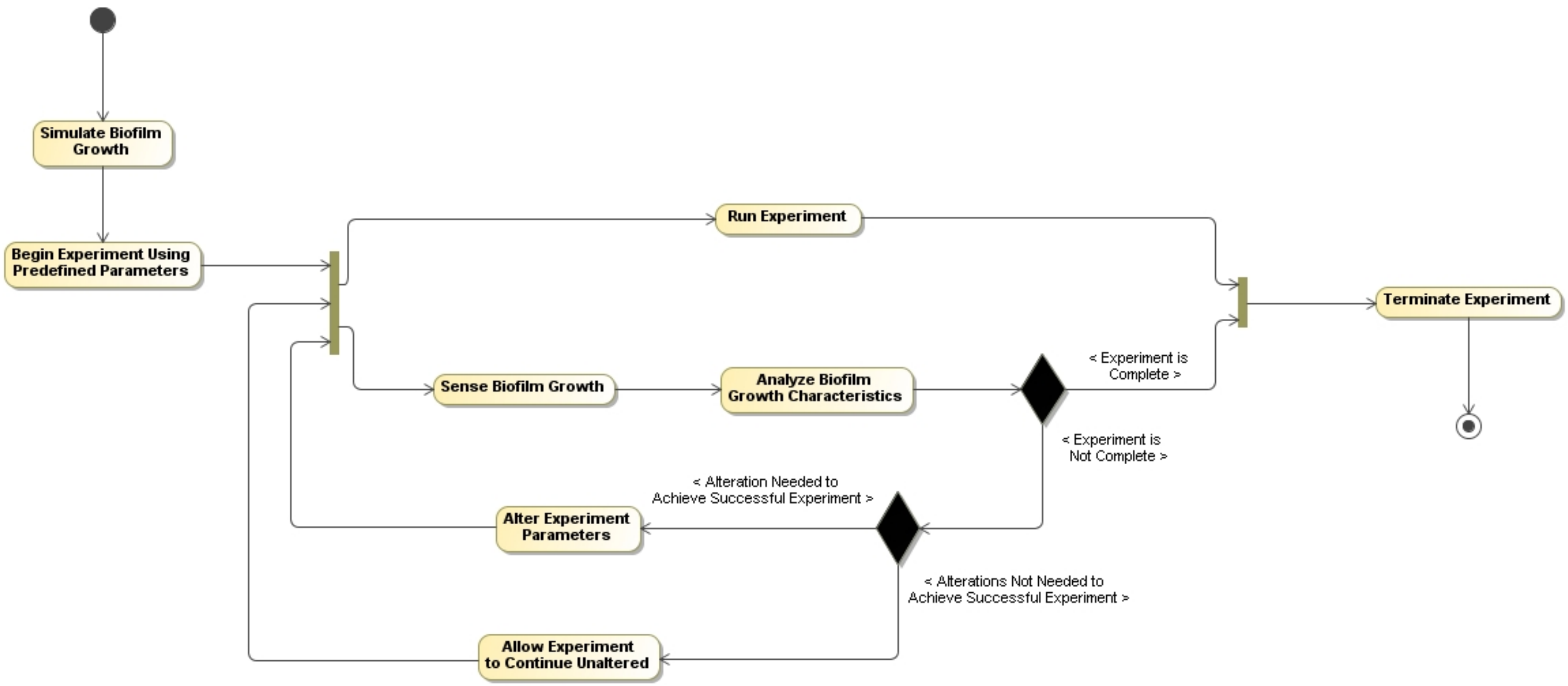
Platform-Level Requirements

Requirement Category	Req. Number	Description
Biofilm Growth Simulation	R1	Input of all critical parameters in simulation (e.g. bacteria type, flow rate, temperature, growth media)
	R2	Simulation software is readily available at low cost
Microfluidic Environment	R1	Integrate fluid environment with prescribed sensing method
	R2	Use of biocompatible materials
	R3	Cost effective process with batch fabrication giving an economy of scale: price <$5.00 / unit
Sensing and Data Processing	R1	Interact with microfluidic growth environment
	R3	Data processing provides output in graphical formats
Experimental Control	R1	Control of all critical experiment parameters (e.g. flow rate, temperature, experiment time)
	R2	Changes in experimental parameters are quantitatively recordable

Use Case Analysis

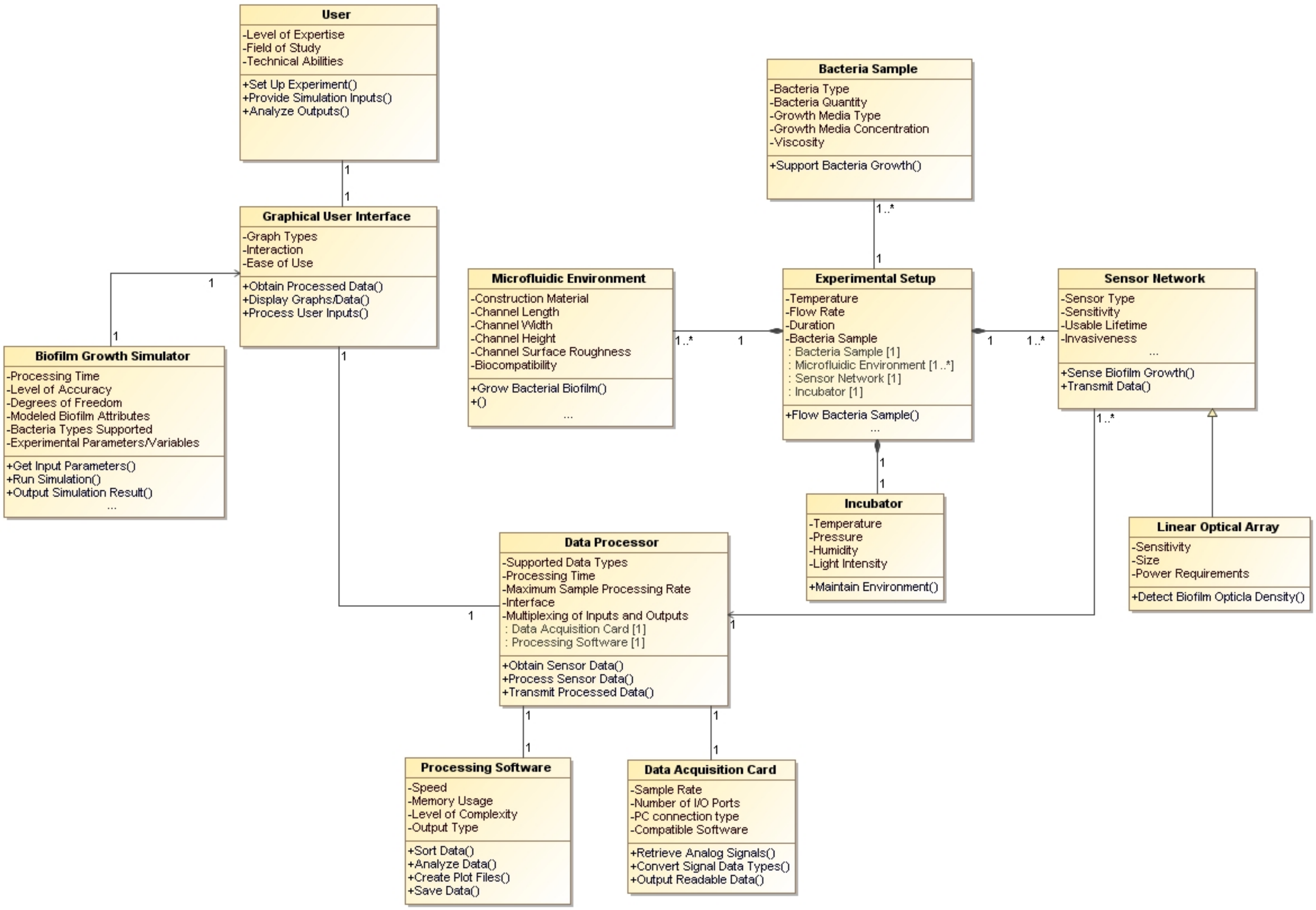


System Behavior Analysis



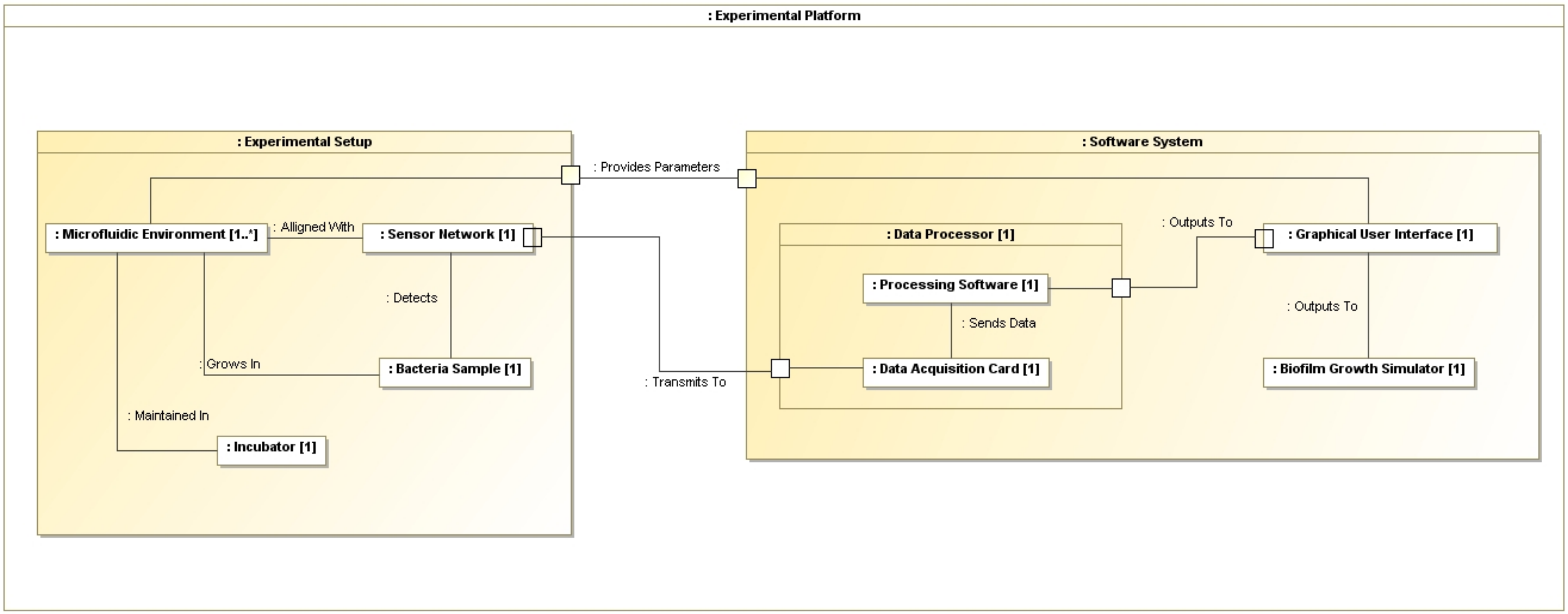
Lower-level activity and sequence diagrams further specify system behaviors !

System Structure Analysis



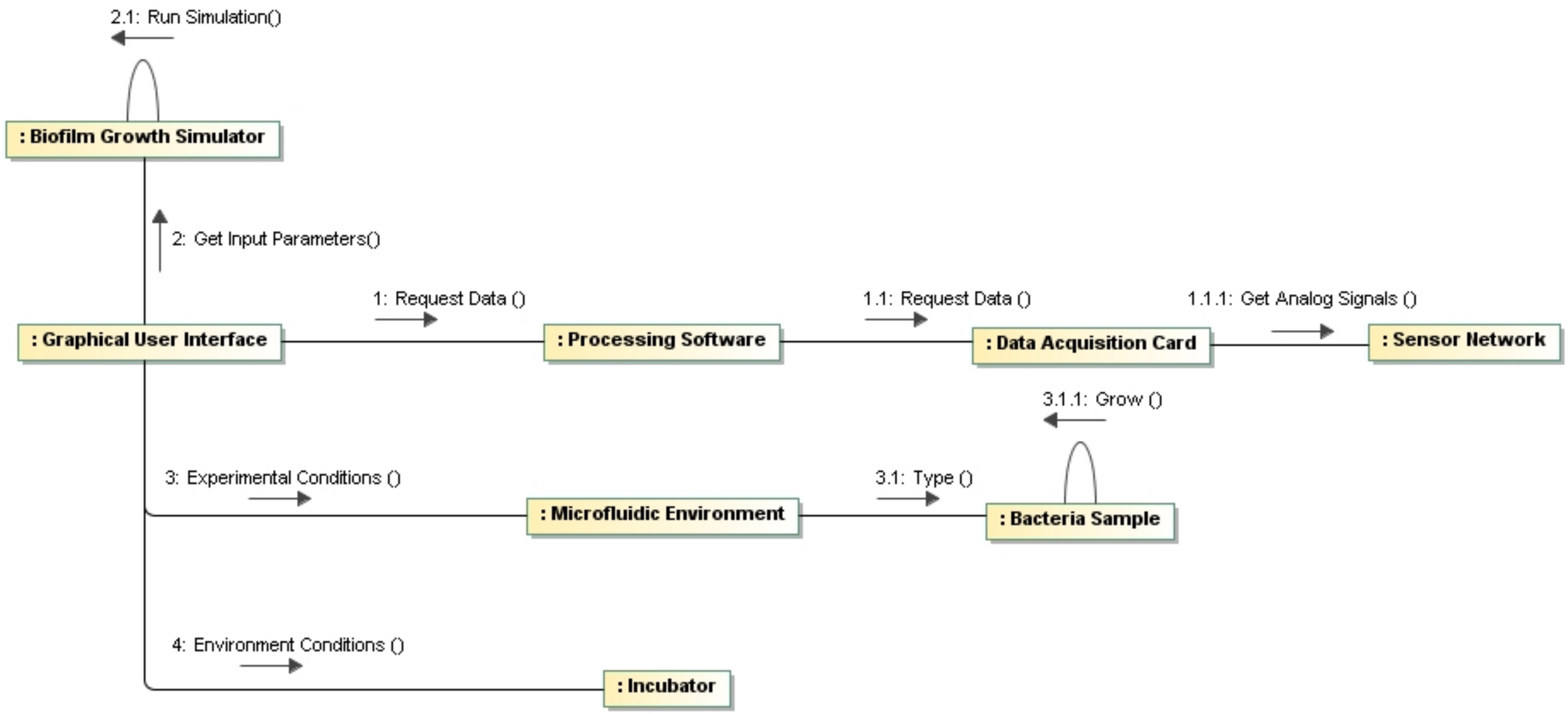
System-Level Design and Integration

Utilize system-level modeling to map system behaviors to a physical system design



Composite-structure diagram shows interfaces between system components and relationships between them

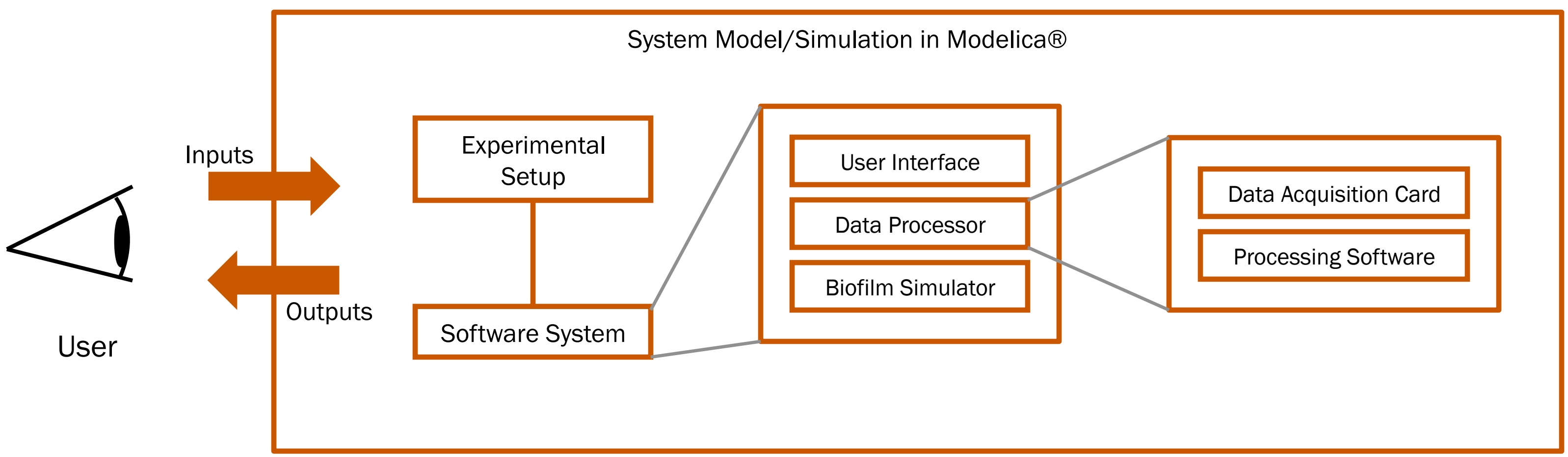
System-Level Design and Integration



Communication diagram shows messages between system components and relative timing of these communications

Library of Reusable Components

- Rationale: to provide a tool for making design decisions for experimental platforms for biofilm studies
- Key Factors
  - Interfacing data transfer and physical coupling of components
  - Measures of effectiveness: cost, versatility, processing time, etc.
    - System-level and component-level measures of effectiveness
  - Parametric tradeoff between various designs



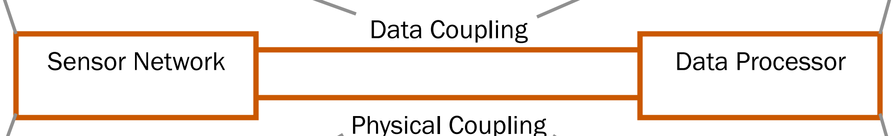
Library of Reusable Components

Example:

cross-hierarchy coupling of a sensor network (experimental system) and a data procsesor (software system)

```
model sensor_network

  physical_coupling a;
  data_coupling b;

  parameter Real
  invasiveness;   parameter
  Real sample_rate;
  parameter Real
  sensitivity;

  protected
  Real network_size;

  equation

end sensor_network;
```

```
connector data_coupling

  Real processing_speed;
  Real data_type;

end data_coupling;
```




```
connector physical_coupling

  Real interface_type;

end physical_coupling;
```

```
model data_processor

  physical_coupling a;
  data_coupling b;

  parameter Real
  process_rate;
  parameter Real
  conversions;

  data_acquisition_card daq;
  processing_software
  data_software;

  protected
  Real file_size;

  equation

end data_processor;
```

Implementation:

```
connect (sensor_network.a, data processor.a);
connect (sensor_network.b, data_processor.b);
```

System Trade-Off Analysis

Type	Option	Cost ($)	Versatility	Performance	Process Time	Repeatability
Sensor Network	SN1	50	0.8	1.2	0.6	0.6
	SN2	100	0.6	1.2	0.4	0.8
Experimental Setup	ES 1	400	0.5	1.3	0.5	0.8
	ES 2	1000	0.9	1.7	0.7	1.0
Data Processor	DP 1	500	0.7	1.2	0.4	0.8
	DP 2	750	0.75	1.4	0.5	0.9
Biofilm Growth Sim	BGS 1	800	0.9	1.0	0.2	0.8
	BGS 2	500	0.4	0.9	0.3	0.6

$$\text{Cost} = C_{SN} + C_{ES} + C_{DP} + C_{BGS}$$

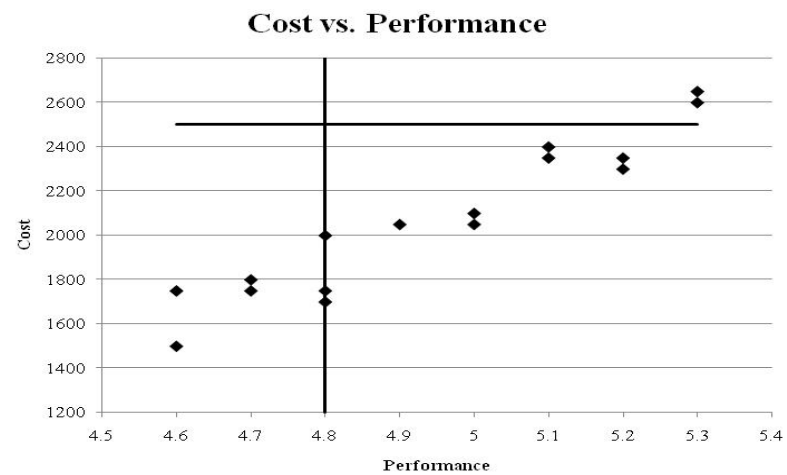
$$\text{Versatility} = V_{SN} + V_{ES} + V_{DP} + V_{BGS}$$

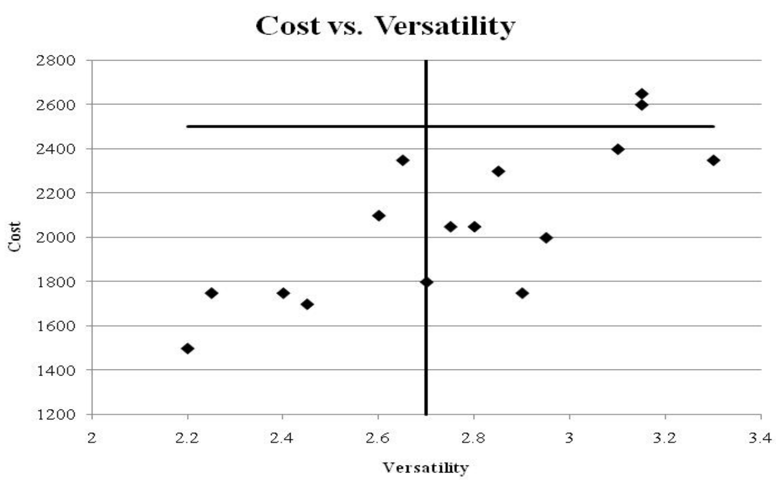
$$\text{Performance} = P_{SN} + P_{ES} + P_{DP} + P_{BGS}$$

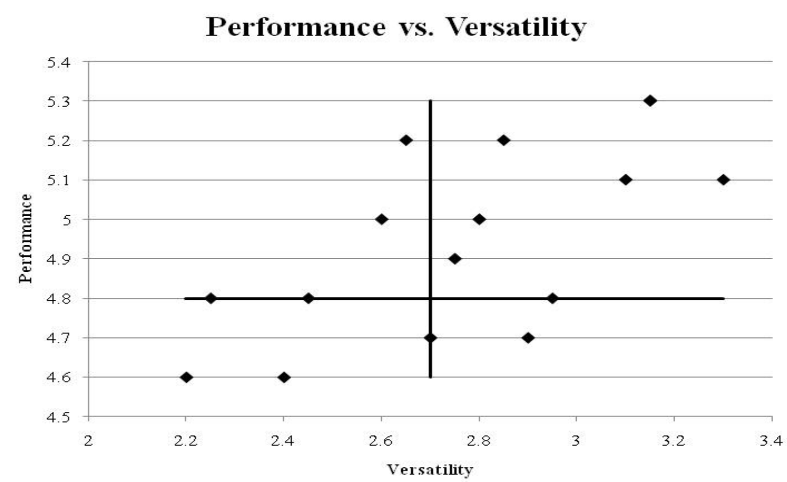
$$P_{XX} = \text{Process Time}_{XX} + \text{Repeatability}_{XX}$$

System Trade-Off Analysis

- 16 Possible Design Configurations
- Soft Constraints
  - Total Cost < $2,500
  - Total Versatility > 2.70
  - Total Performance > 4.80







System Trade-Off Analysis

Trade-Off Curve	Points of Interest
Cost vs. Performance	3, 4, 6, 11, 12, 15, 16
Cost vs. Versatility	1, 3, 4, 5, 6, 11, 15
Performance vs. Versatility	3, 4, 6, 7, 11, 15
Overall	**3, 4, 6, 11, 15**

Design No.	Cost	Versatility	Performance
~~**3**~~	~~2350~~	~~3.3~~	~~5.1~~
~~**4**~~	~~2400~~	~~3.1~~	~~5.1~~
~~**6**~~	~~2050~~	~~2.75~~	~~4.9~~
11	2050	2.8	5.0
~~**15**~~	~~2300~~	~~2.85~~	~~5.2~~

Design Comparisons

- 3 vs. 4
  - 3 wins (less cost & better versatility)
- 6 vs. 11
  - 11 wins (increase in performance & versatility for less cost)
- 3 vs. 15
  - 3 wins (15.8% increase in versatility, 1.9% increase in performance, only 2.2% cost increase)
- 3 vs. 11
  - 11 wins (17.8% increase in versatility but at a cost increase of 14.6%. Cost is more important than versatility)

Design Option 11			
Component Selection		**Performance Characteristics**	
Sensor Network	SN 1	Cost	$2050
Experimental Setup	ES 2	Versatility	2.8
Data Processor	DP 1	Process Time	2.0
Biofilm Growth Sim	BGS 2	Repeatability	3.0

Conclusions

1. Developed system-level design of a bacterial biofilm experimental platform
   - System behavior
   - System structure
   - System Integration
2. Created a basis for a library of reusable components using the Modelica® language
   - Tool to streamline the design of similar systems
3. Trade-off analysis of system measures of effectiveness

Thank You

Questions

References

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