

Slides, videos, links and more:

<https://github.com/physicell-training/ws2022>

Session 13: Intracellular with libRoadrunner (interactive demo)



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PhysiCell Project

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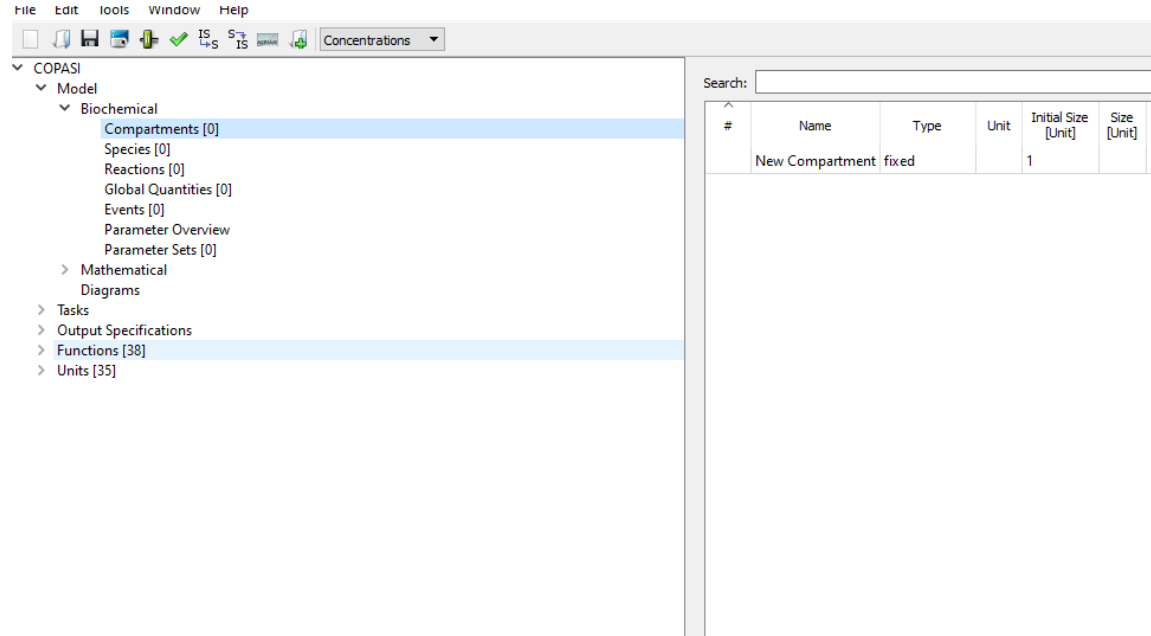
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Agenda

- SBML Creation
- Adding Intracellular integrations
- Let's code together

SBML Creation

- We need to create our SBML
- Let's start our Copasi



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SBML Creation

- We will start with compartments
- Let's add “Intracellular” compartment
- Volume = 1.0

COPASI 4.24 (Build 197)

File Edit Tools Window Help

Concentrations

Search:

#	Name	Type	Unit	Initial Size [Unit]	Size [Unit]	Rate [Unit/s]	Initial Expression [Unit]	Expression [Unit] or [Unit/s]	Noise Expression
1	Intracellular	fixed	ml	1	nan	0			
	New Compartment	fixed		1					

Model

- Biochemical
 - Compartments [1]
 - Species [0]
 - Reactions [0]
 - Global Quantities [0]
 - Events [0]
 - Parameter Overview
 - Parameter Sets [0]
- Mathematical
 - Diagrams
- Tasks
- Output Specifications
- Functions [38]
- Units [35]

SBML Creation : Species

- There will be 8 Species

Search:

#	Name	Compartment	Type	Unit	Initial Concentration [Unit]	Concentration [Unit]	Rate [Unit/min]	Initial Expression [Unit]	Expression [Unit] or [Unit/min]	Noise Expression
1	Glucose	Intracellular	reactions	mmol/ml	100	nan	nan			
2	Oxygen	Intracellular	reactions	mmol/ml	100	nan	nan			
3	Energy	Intracellular	reactions	mmol/ml	450	nan	nan			
4	Lactate	Intracellular	reactions	mmol/ml	0	nan	nan			
5	apoptosis_rate	Intracellular	reactions	mmol/ml	0	nan	nan			
6	migration_speed	Intracellular	reactions	mmol/ml	0	nan	nan			
7	Lac_Secretion_Rate	Intracellular	reactions	mmol/ml	0	nan	nan			
8	Transition_Rate	Intracellular	reactions	mmol/ml	0	nan	nan			
	New Species	Intracellular	reactions	mmol/ml	1					

SBML Creation : Reactions

- There will be three Reactions

Search: <input type="text"/>					
^ #	Name	Reaction	Rate Law	Flux [mmol/min]	Noise Expression
1	Aerobic	Glucose + 6 * Oxygen -> 38 * Energy	Mass action (irreversible)	nan	
2	Anaerobic	Glucose -> 2 * Energy + Lactate	Mass action (irreversible)	nan	
3	Energy_Usage	Energy ->	Mass action (irreversible)	nan	
	New Reaction				



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SBML Creation : Global Quantities

- There will be 6 Global Quantities

Search: <input type="text"/>									
#	Name	Type	Unit	Initial Value [Unit]	Transient Value [Unit]	Rate [Unit/min]	Initial Expression [Unit]	Expression [Unit] or [Unit/min]	Noise Expression
1	k_aer	fixed	?	0.01	nan	0			
2	k_ane	fixed	?	0.00018	nan	0			
3	k_usage	fixed	?	0.0023	nan	0			
4	energy_move_thresh	fixed	?	440	nan	0			
5	energy_death_thresh	fixed	?	430	nan	0			
6	energy_prolif_thresh	fixed	?	445	nan	0			
	New Quantity	fixed		0					

SBML Creation: Events

- 6 Events to create

Search: <input type="text"/>						
#	Name	Trigger Expression	Delayed	Delay Expression	Assignment Target	Assignment Expression
1	die	[Energy] lt Values[energy_death_thresh]	Assignment	0	apoptosis_rate	8.999999999999999e+99
2	do_not_move	[Energy] gt Values[energy_move_thresh]	Assignment	0	migration_speed	0
3	move	[Energy] lt Values[energy_move_thresh]	Assignment	0	migration_speed	10
4	Lac_Sec	[Lactate] gt 0.01	Assignment	0	Lac_Secretion_Rate	0.0001
5	divide	[Energy] gt Values[energy_prolif_thresh]	Assignment	0	Transition_Rate	0.00016666660000000001
6	do_not_divide	[Energy] lt Values[energy_prolif_thresh]	Assignment	0	Transition_Rate	0
	New Event					



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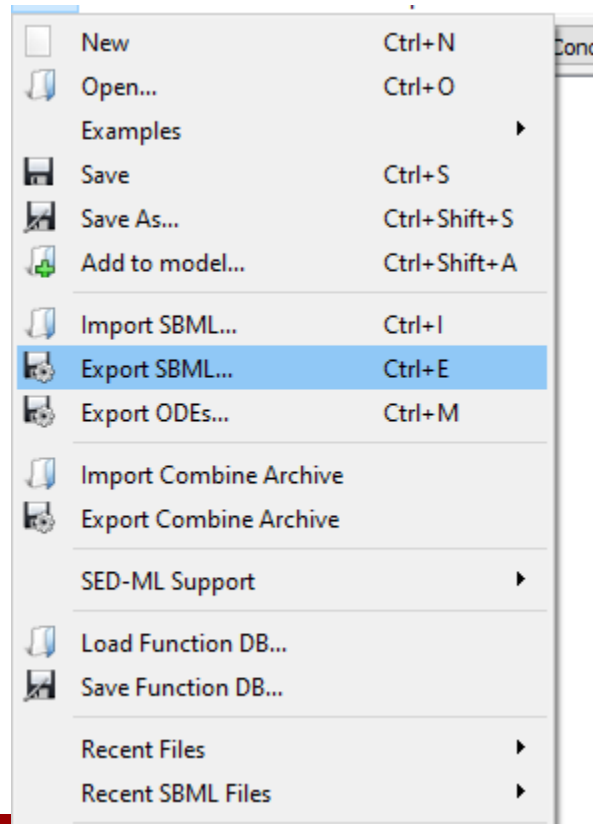
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SBML Creation : Save



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Agenda

- SBML Creation
- Adding Intracellular integrations
- Let's code together

Let's Add Intracellular Attribute

```
<intracellular type="roadrunner">
```

```
  <sbml_filename>./config/Toy_Metabolic_Model.xml</sbml_filename>
```

```
    <map PC_substrate="oxygen" sbml_species="Oxygen"></map >
```

```
    <map PC_substrate="lactate" sbml_species="Lactate"></map >
```

```
    <map PC_substrate="glucose" sbml_species="Glucose"></map >
```

```
    <map PC_phenotype="da" sbml_species="apoptosis_rate"></map>
```

```
    <map PC_phenotype="mms" sbml_species="migration_speed"></map>
```

```
    <map PC_phenotype="ssr_lactate" sbml_species="Lac_Secretion_Rate"></map>
```

```
    <map PC_phenotype="ctr_0_0" sbml_species="Transition_Rate"></map>
```

```
</intracellular>
```

```

</cell_interactions>

<cell_transformations>
  <transformation_rates>
    <transformation_rate name="default" units="1/min">0.0</transformation_rate>
  </transformation_rates>
</cell_transformations>

<intracellular type="roadrunner">
  <sbml_filename>./config/Toy_Metabolic_Model.xml</sbml_filename>
  <map PC_substrate="oxygen" sbml_species="Oxygen"></map >
  <map PC_substrate="lactate" sbml_species="Lactate"></map >
  <map PC_substrate="glucose" sbml_species="Glucose"></map >
  <map PC_phenotype="da" sbml_species="apoptosis_rate"></map>
  <map PC_phenotype="mms" sbml_species="migration_speed"></map>
  <map PC_phenotype="ssr_lactate" sbml_species="Lac_Secretion_Rate"></map>
  <map PC_phenotype="ctr_0_0" sbml_species="Transition_Rate"></map>
</intracellular>

</phenotype>
<custom_data>
  <intra_oxy conserved="false" description="" units="dimensionless">0.0</intra_oxy>
  <intra_glu conserved="false" description="" units="a.u">0.0</intra_glu>
  <intra_lac conserved="false" description="" units="a.u">0.0</intra_lac>
  <intra_energy conserved="false" description="" units="a.u">0.0</intra_energy>
</custom_data>
</cell_definition>

```



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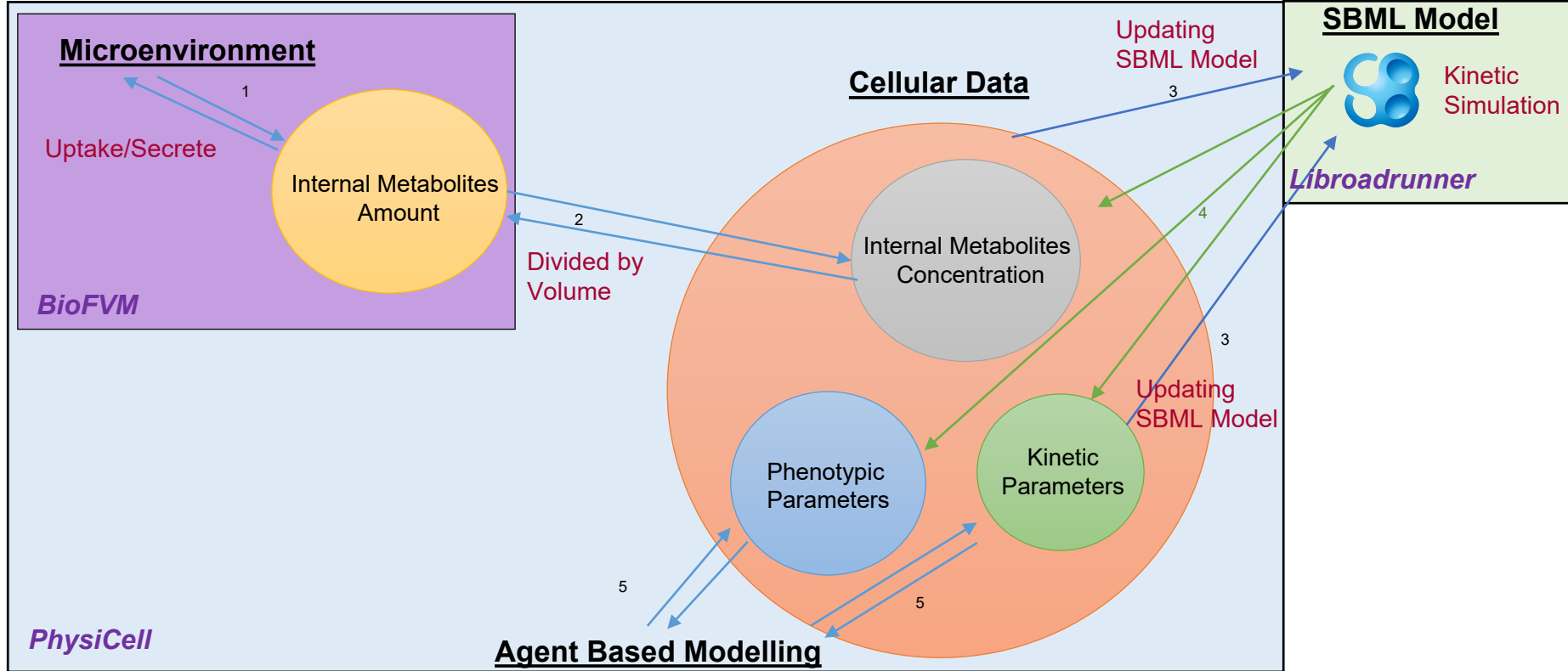
Let's edit custom module

- Setup_tissue()

```
// let's set initial intracellular custom data according to config specifications
set_single_behavior( pCell , "custom:intra_oxy" , parameters.doubles("initial_internal_oxygen" ));
set_single_behavior( pCell , "custom:custom:intra_glu" , parameters.doubles("initial_internal_glucose"));
set_single_behavior( pCell , "custom:custom:intra_lac" , parameters.doubles("initial_internal_lactate"));
set_single_behavior( pCell , "custom:custom:intra_energy" , parameters.doubles("initial_energy" ));

// set the internalized values
double cell_volume = get_single_signal( pCell , "volume");
pCell->phenotype.molecular.internalized_total_substrates[oxygen_substrate_index]= get_single_signal( pCell ,
"custom:intra_oxy") * cell_volume;
pCell->phenotype.molecular.internalized_total_substrates[glucose_substrate_index]= get_single_signal( pCell ,
"custom:intra_glu") * cell_volume;
pCell->phenotype.molecular.internalized_total_substrates[lactate_substrate_index]= get_single_signal( pCell ,
"custom:intra_lac") * cell_volume;
(*all_cells)[i]->phenotype.intracellular->set_parameter_value("Energy",get_single_signal( pCell ,
"custom:intra_energy"));
```

Integration Design



Update Intracellular

- Let's start changing update_intracellular()

```
void update_intracellular(){    // BioFVM Indices
static int oxygen_substrate_index = microenvironment.find_density_index( "oxygen" );
static int glucose_substrate_index = microenvironment.find_density_index( "glucose" );
static int lactate_substrate_index = microenvironment.find_density_index( "lactate");
```



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For loop for all cells

```
#pragma omp parallel for
for( int i=0; i < (*all_cells).size(); i++ )
{
    if( (*all_cells)[i]->is_out_of_domain == false )
    {

    }
}
```



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Let's start filling

- ```
#pragma omp parallel for
for(int i=0; i < (*all_cells).size(); i++)
{
 // Custom Data Indices
 static int i_Oxy_i = (*all_cells)[i]->custom_data.find_variable_index("intra_oxy");
 static int i_Glu_i = (*all_cells)[i]->custom_data.find_variable_index("intra_glu");
 static int i_Lac_i = (*all_cells)[i]->custom_data.find_variable_index("intra_lac");
 static int energy_vi = (*all_cells)[i]->custom_data.find_variable_index("intra_energy");
 if((*all_cells)[i]->is_out_of_domain == false)
 {

 }
}
```



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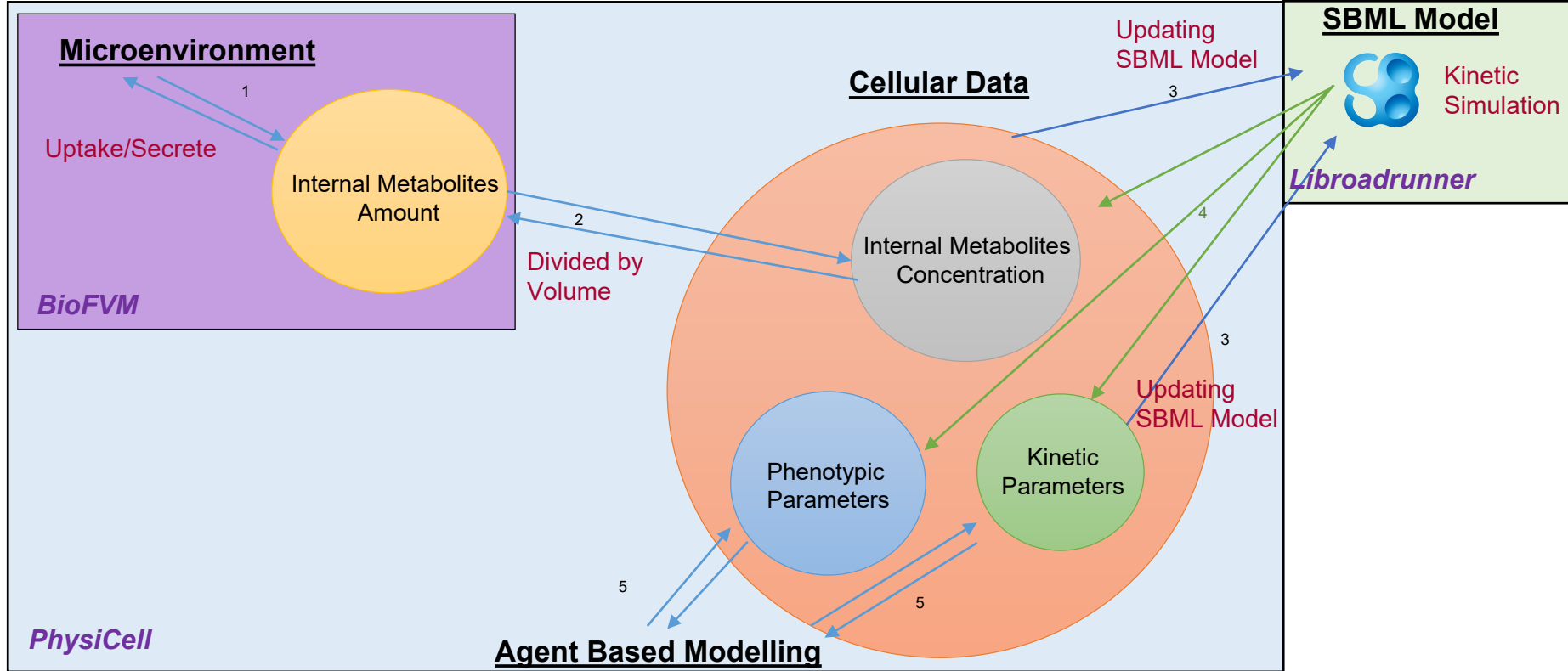
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# Integration Design



# Update SBML

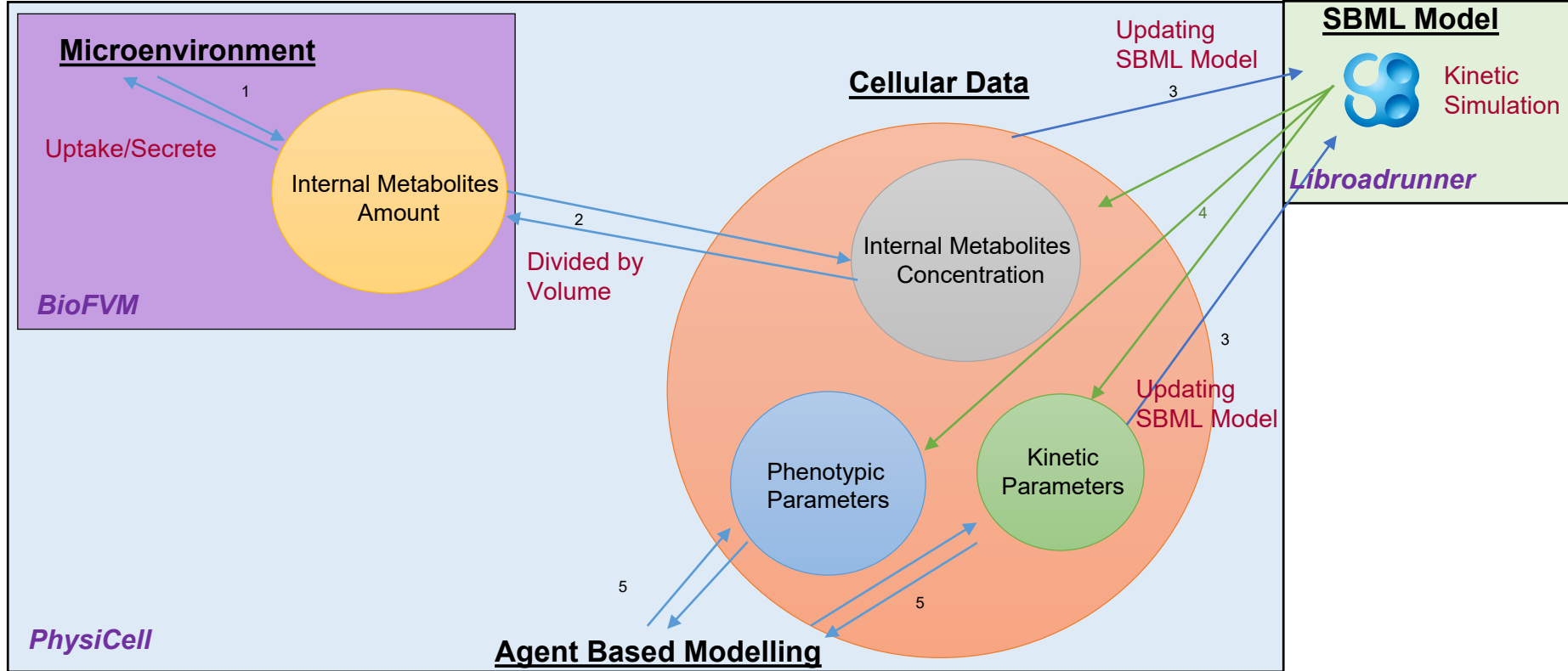
```
if((*all_cells)[i]->is_out_of_domain == false)
{
 // Cell Volume
 double cell_volume = (*all_cells)[i]->phenotype.volume.total;

 // Intracellular Concentrations
 double oxy_val_int = (*all_cells)[i]-
 >phenotype.molecular.internalized_total_substrates[oxygen_substrate_index]/cell_volume;
 double glu_val_int = (*all_cells)[i]-
 >phenotype.molecular.internalized_total_substrates[glucose_substrate_index]/cell_volume;
 double lac_val_int = (*all_cells)[i]-
 >phenotype.molecular.internalized_total_substrates[lactate_substrate_index]/cell_volume;

 // Update SBML
 (*all_cells)[i]->phenotype.intracellular->set_parameter_value("Oxygen",oxy_val_int);
 (*all_cells)[i]->phenotype.intracellular->set_parameter_value("Glucose",glu_val_int);
 (*all_cells)[i]->phenotype.intracellular->set_parameter_value("Lactate",lac_val_int);

 ...
}
```

# Integration Design



# SBML Simulation

...

// SBML Simulation

```
(*all_cells)[i]->phenotype.intracellular->update();
```

// Phenotype Simulation

```
(*all_cells)[i]->phenotype.intracellular->update_phenotype_parameters((*all_cells)[i] ->phenotype);
```

...



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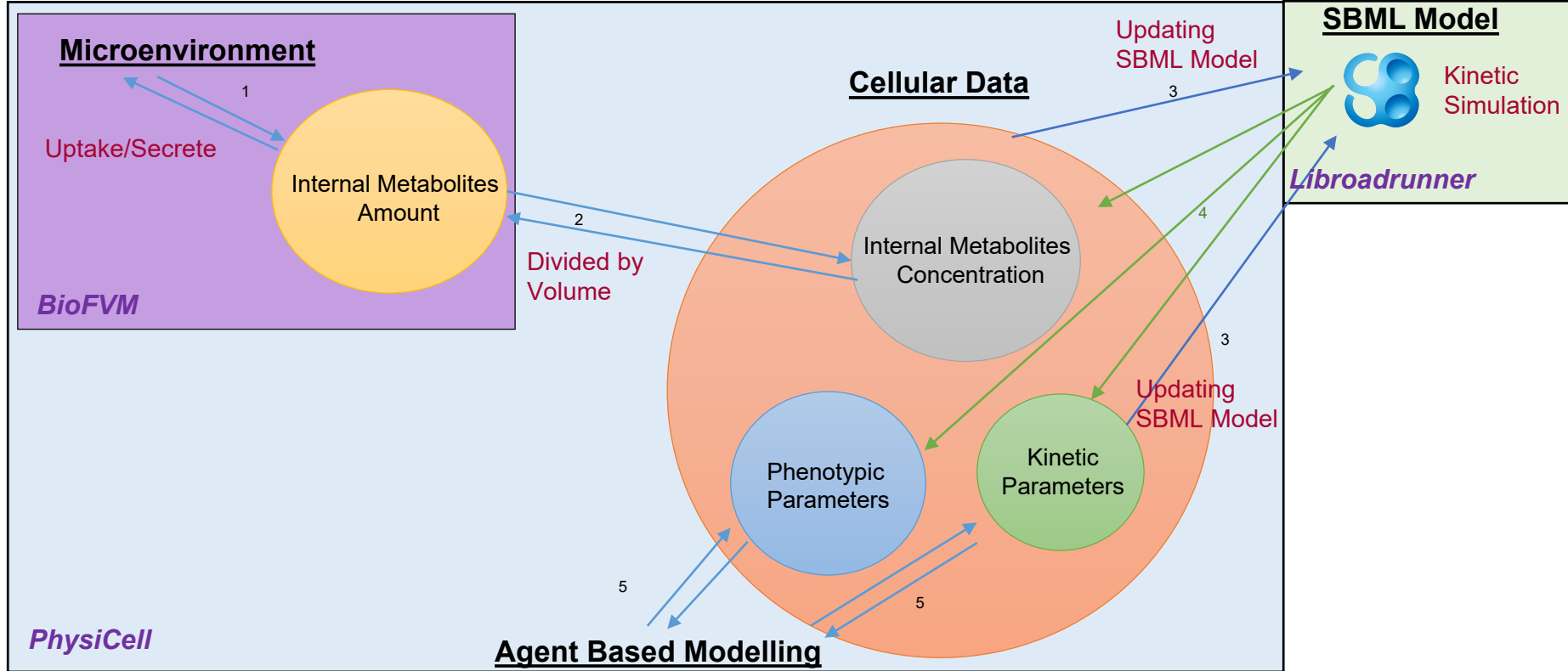
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# Integration Design



# Update PhysiCell

...

// Internalized Chemical Update After SBML Simulation

```
(*all_cells)[i]->phenotype.molecular.internalized_total_substrates[oxygen_substrate_index] = (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Oxygen") * cell_volume;
(*all_cells)[i]->phenotype.molecular.internalized_total_substrates[glucose_substrate_index] = (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Glucose") * cell_volume;
(*all_cells)[i]->phenotype.molecular.internalized_total_substrates[lactate_substrate_index] = (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Lactate") * cell_volume;
```

//Save custom data

```
(*all_cells)[i]->custom_data[i_Oxy_i] = (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Oxygen");
(*all_cells)[i]->custom_data[i_Glu_i] = (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Glucose");
(*all_cells)[i]->custom_data[i_Lac_i] = (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Lactate");
(*all_cells)[i]->custom_data[energy_vi] = (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Energy");
}
```



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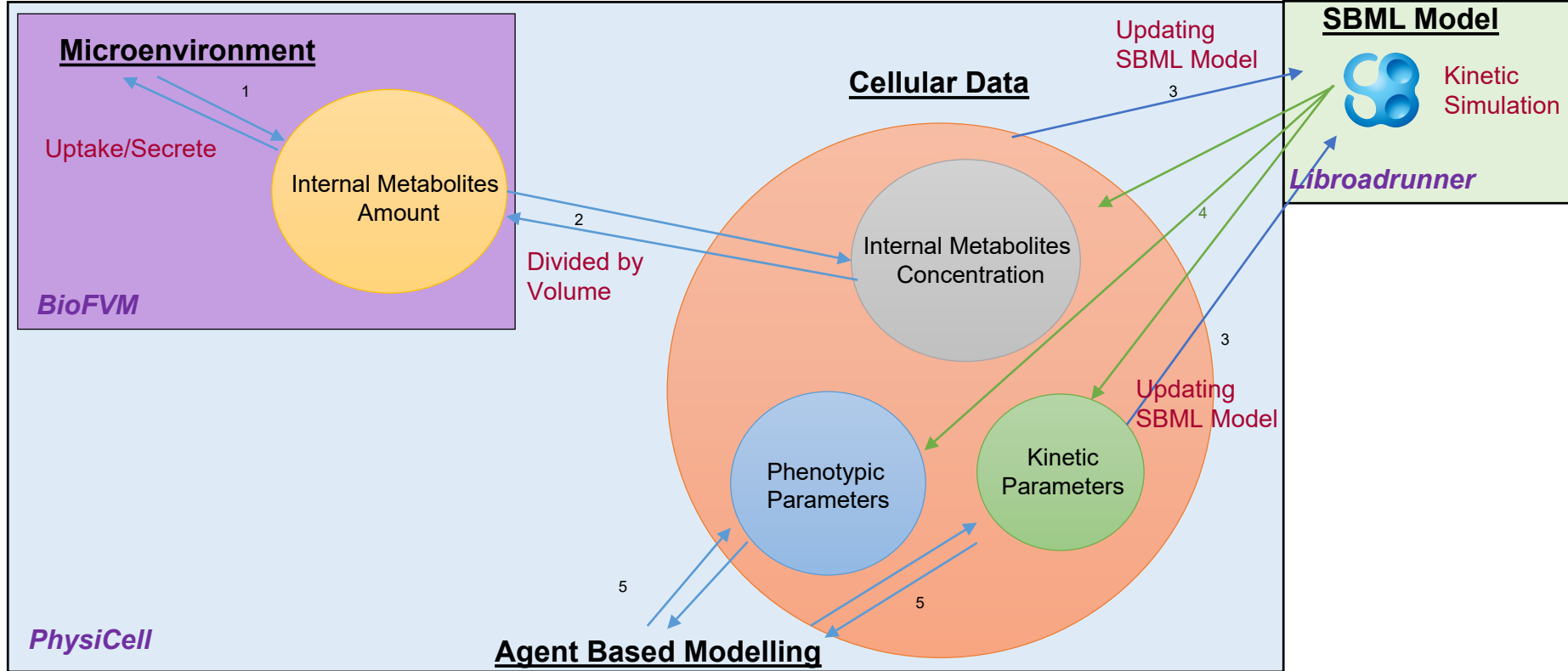
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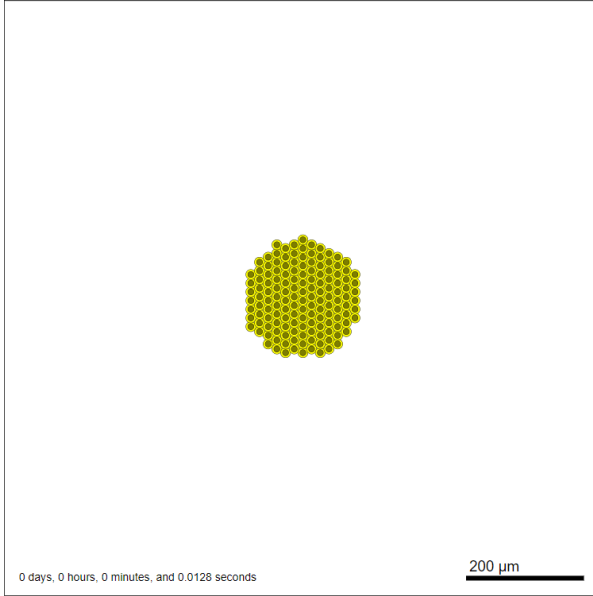
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# Integration Design

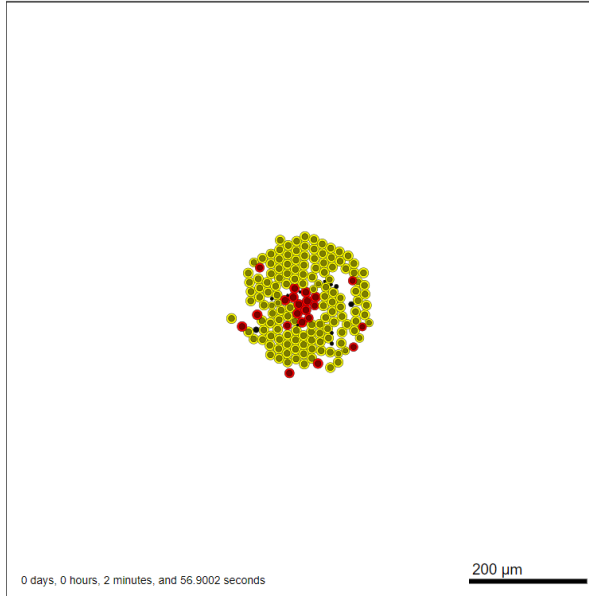




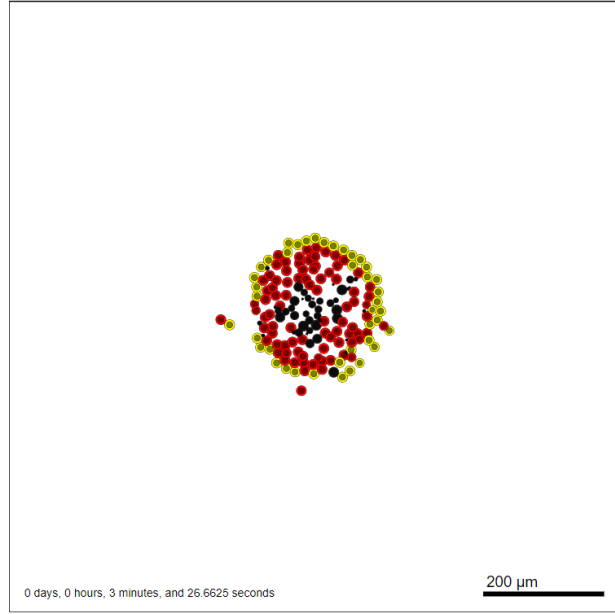
Current time: 0 days, 0 hours, and 0.00 minutes,  $z = 0.00 \mu\text{m}$   
144 agents



Current time: 0 days, 11 hours, and 0.00 minutes,  $z = 0.00 \mu\text{m}$   
168 agents



Current time: 0 days, 13 hours, and 0.00 minutes,  $z = 0.00 \mu\text{m}$   
171 agents



# Different Intracellular\_dt

- Let's change intracellular\_dt
- Demo



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# Up next

- End of live sessions for today.
- Two async sessions left
- Let's meet at the Hackathon for the first Team Time



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# Funding Acknowledgements



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The Common  
Fund



leidos



## PhysiCell Development:

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