

Slides, videos, links and more:

<https://github.com/physicell-training/ws2023>

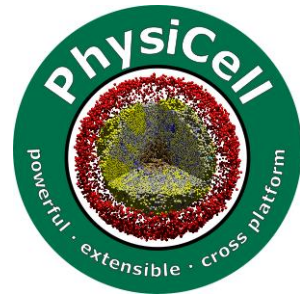
Advanced Session 7: Intracellular with libRoadrunner (interactive demo)

Furkan Kurtoglu

 [@PhysiCell](https://twitter.com/PhysiCell)

PhysiCell Project

August 2023



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Logistics

- This is an interactive demo session
- You can stop me during the presentation if you have any question
- Due to limited time SBML-creation will not be covered.
 - Please follow previous years tutorial
 - <https://youtu.be/IMtG44cJejM?t=1691>
- In this session we will be using PhysiCell studio to create config file.
- Rest of it will be on coding including running
- It is a slightly simple model than “ode-energy-sample” model
 - No cycling

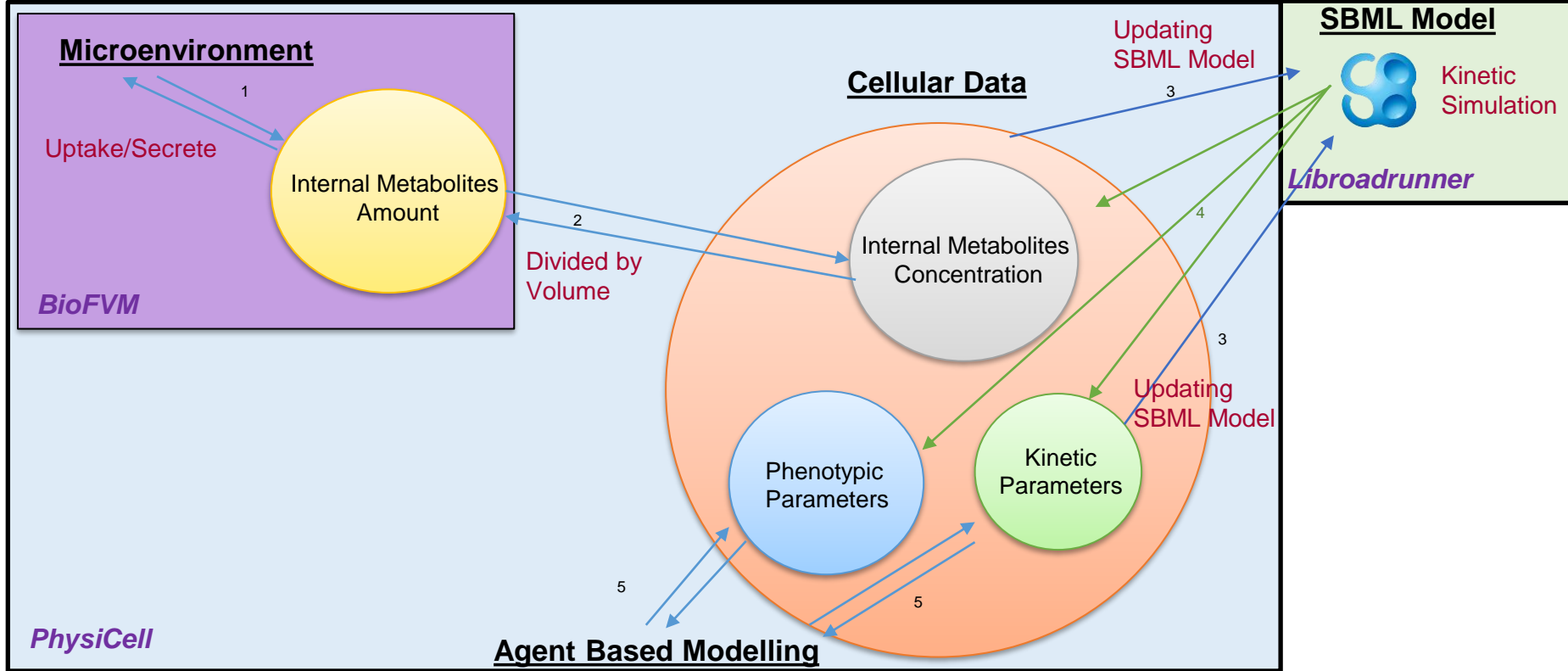
Agenda:

- Previous Session
 - Integration
 - Tokens
- Model Description
- SBML Model
 - Copasi Exploration
- SBML Integration in PhysiCell
- Simulation & Analysis

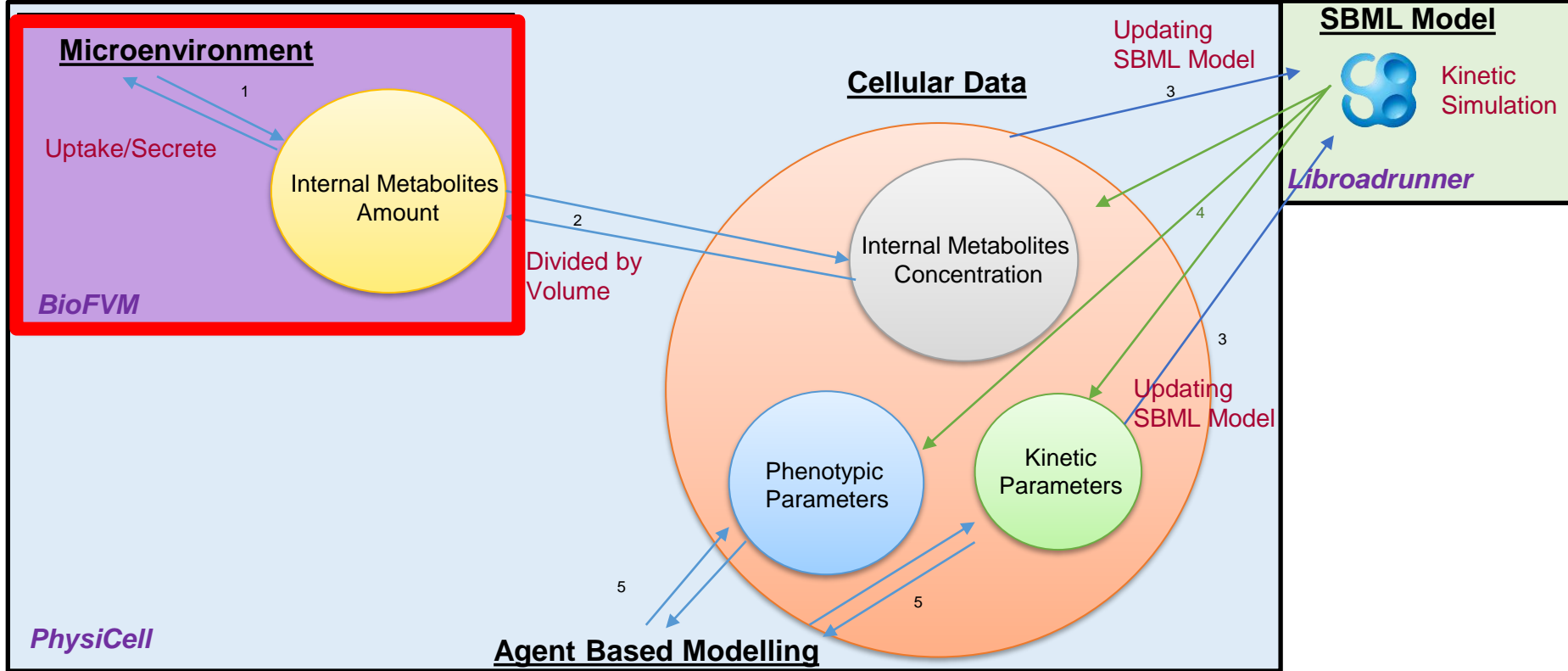
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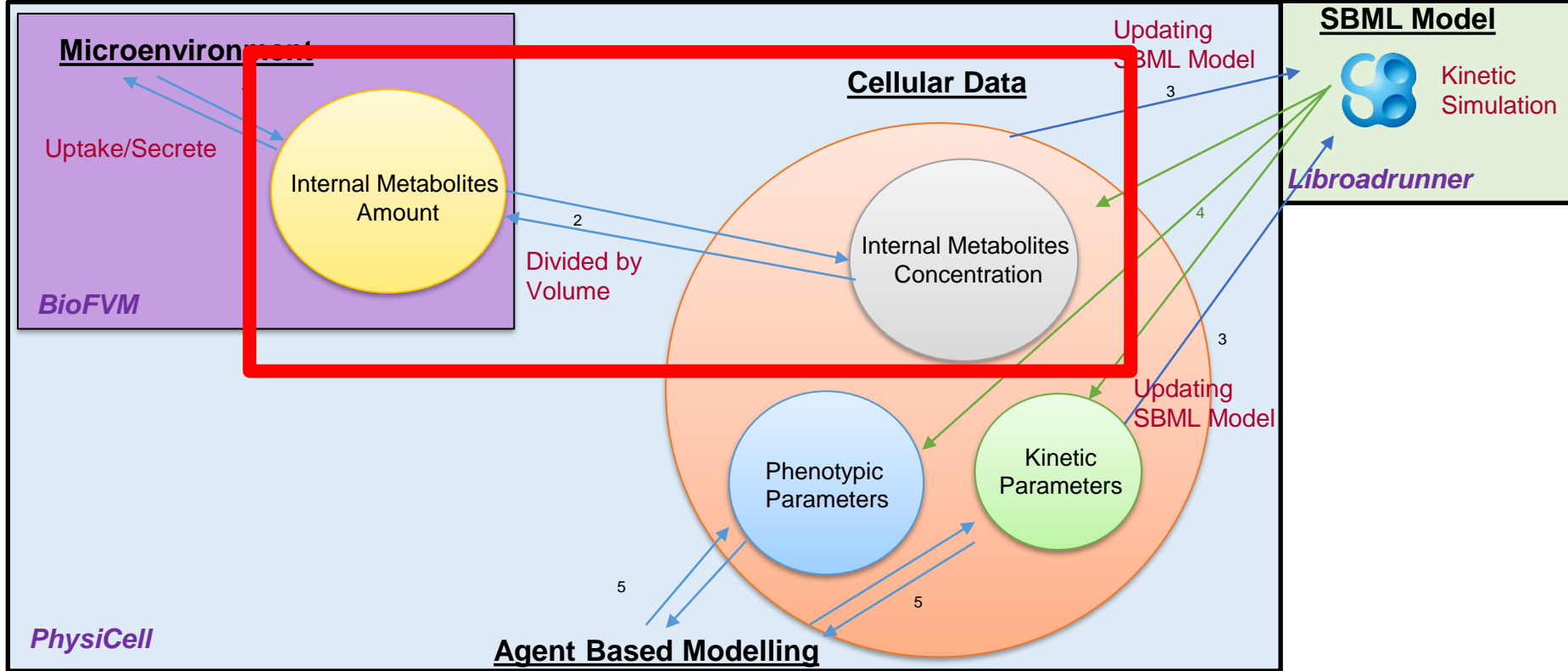
Integration Design



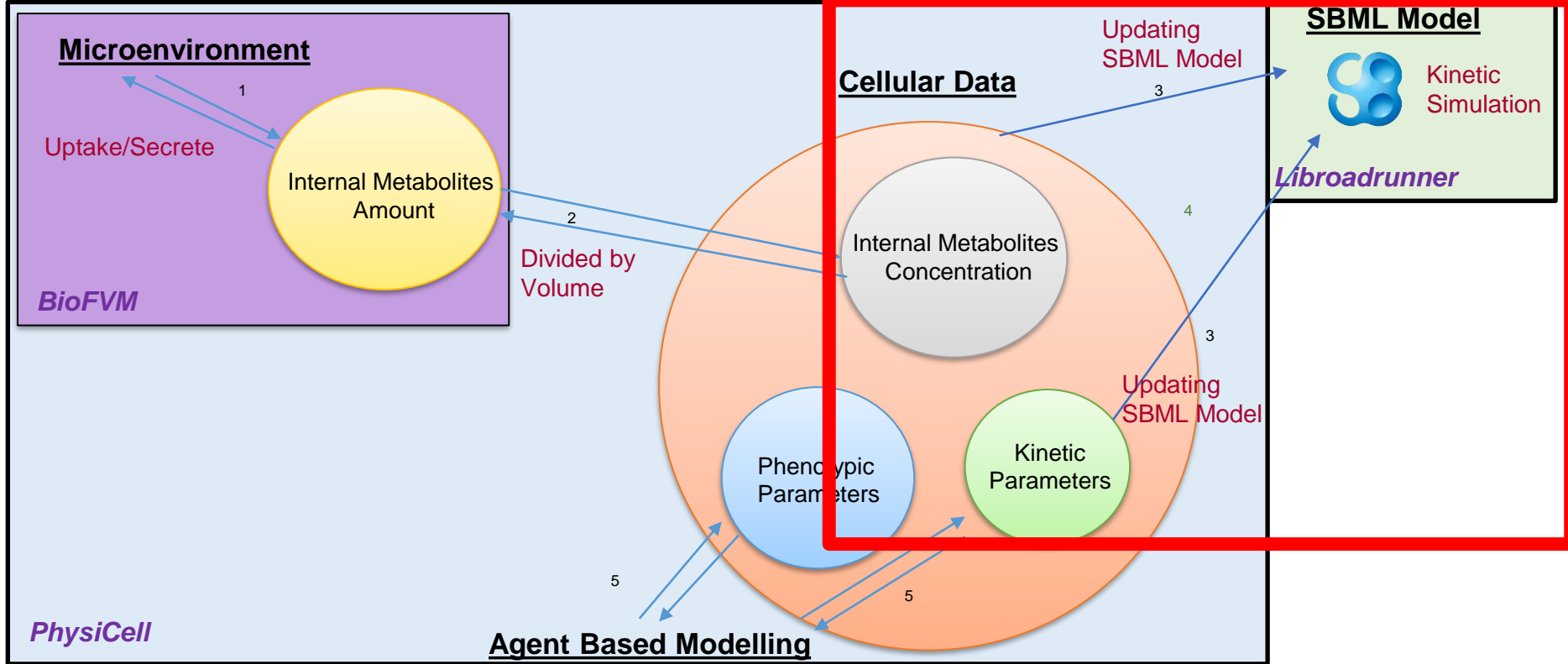
Integration Design



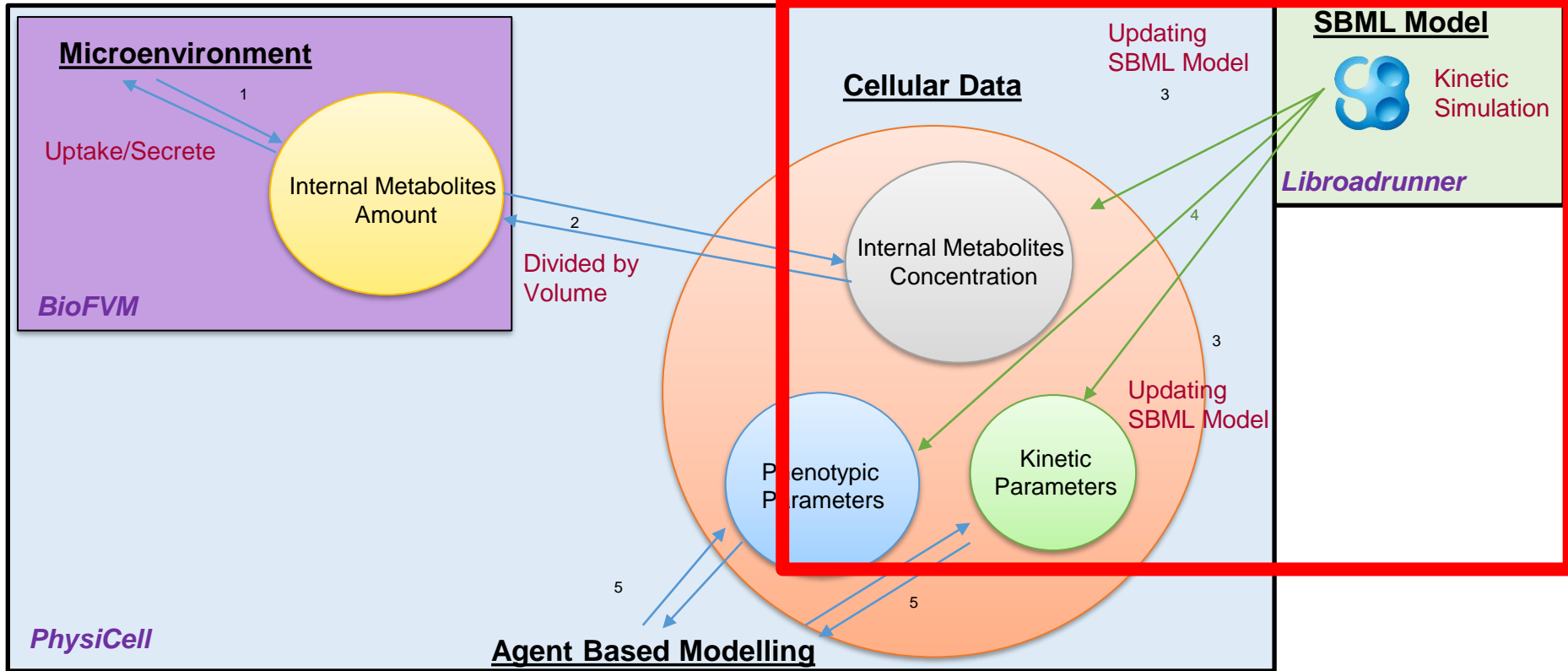
Integration Design



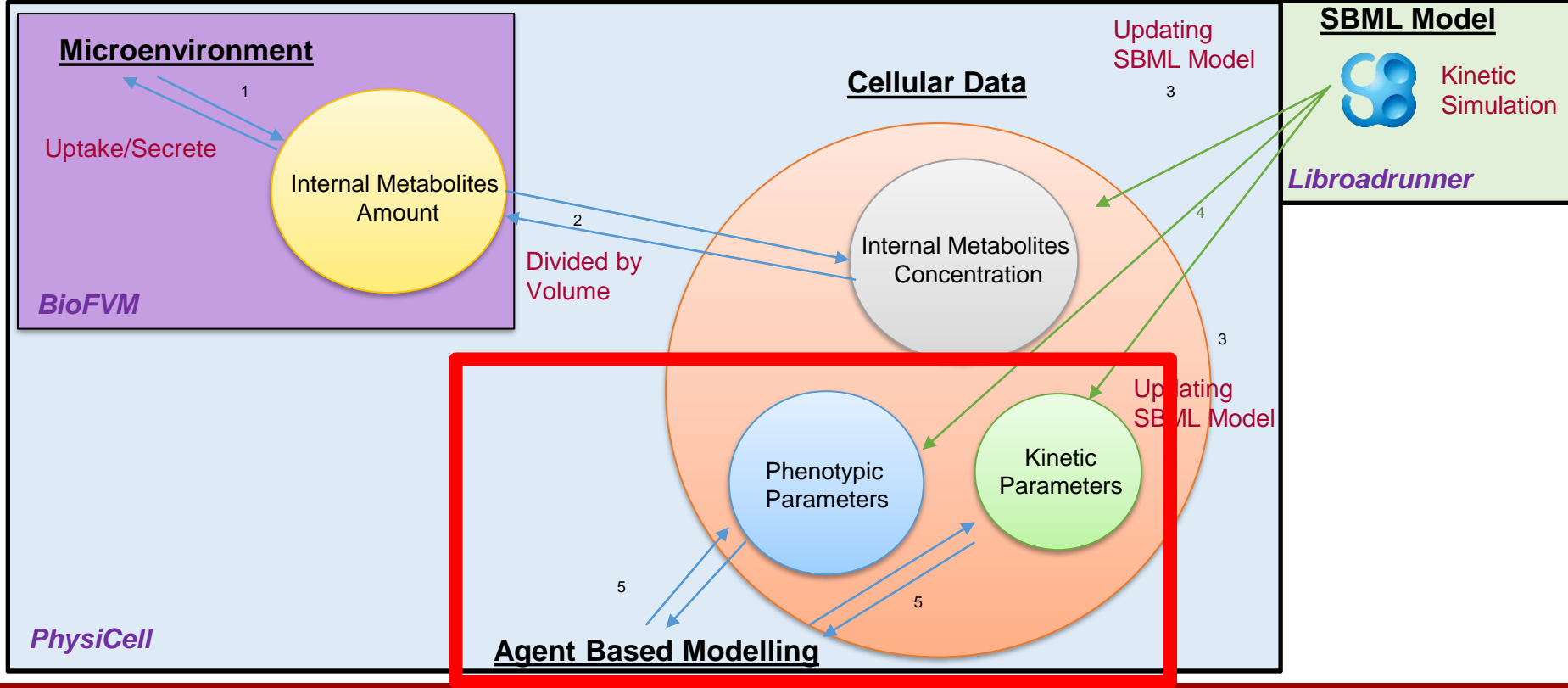
Integration Design



Integration Design



Integration Design



SBML-Phenotypic Parameters

PhysiCell Phenotype Parameter	First letter	phenotype_token	example
Phase Transition Rate	c	ctr_**	ctr_0_1
Death Rate	d	da,dn	da,dn
Persistence Time	m	mpt	mpt
Migration Speed	m	mms	mms
Migration Bias	m	mmb	mmb
Uptake rate	s	sur_*	sur_oxygen
Secretion rate	s	ssr_*	ssr_glucose
Saturation density	s	ssd_*	ssd_oxygen
Export rate	s	ser_*	ser_lactate
Target solid cytoplasmic	v	vtsc	vtsc
Target solid nuclear	v	vtsn	vtsn
Target fluid fraction	v	vff	vff



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LibRoadRunner Interactive Demo



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SBML Model

- Three Substrates
 - Oxygen, Glucose, Lactate
 - Energy is created with two reactions
 - ♦ $\text{Glucose} + \text{Oxygen} \rightarrow 38 * \text{Energy}$ (Aerobic)
 - ♦ $\text{Glucose} \rightarrow 4 * \text{Energy} + \text{Lactate}$ (Anaerobic)
 - Energy consumes
 - ♦ $\text{Energy} \rightarrow$ (Energy_Usage)
- Phenotypic Tokens
 - migration speed, apoptosis_rate, lac_Secretion_Rate

Please be aware this is a toy model to show libRR capability. Parameters are not scientifically estimated.

Model Rules

- Initial Energy = 450
- If Energy > 445
 - Yellow
- If Energy < 440
 - Motile
- If Energy < 430
 - Die



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Generic Workflow

- Create (we will browse) SBML on Copasi
- Create the model domain in the PhysiCell Studio
 - Config Basics
 - Microenvironment
 - Cell parameters
- Integrate SBML to PhysiCell model

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SBML Exploration



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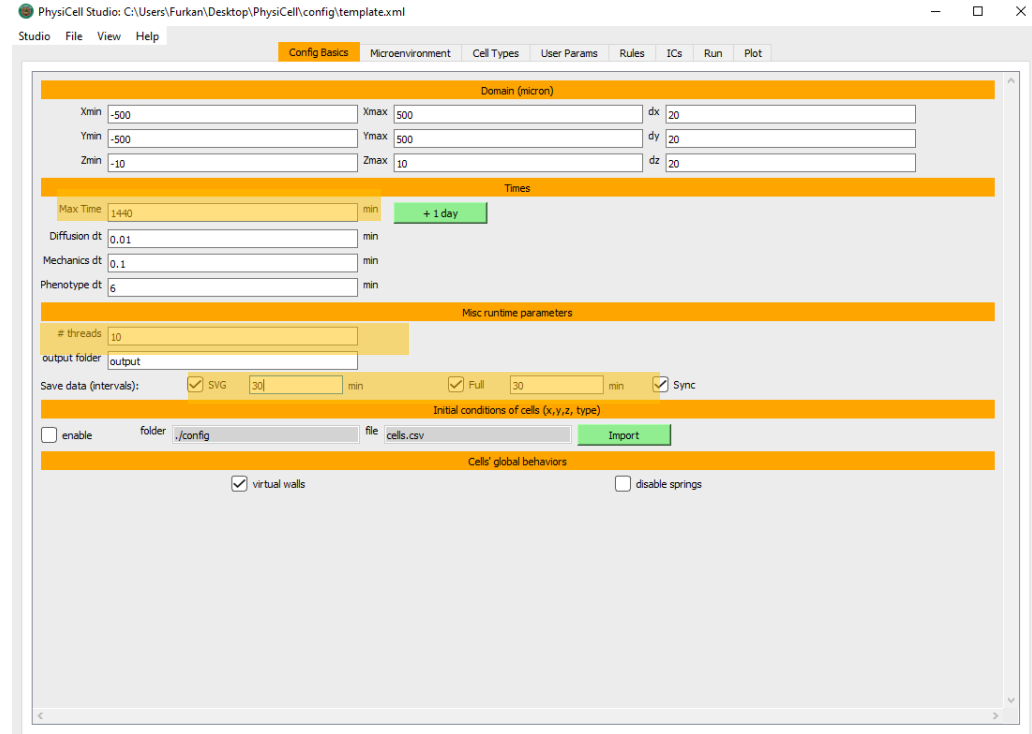
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Agenda:

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- **SBML Integration in PhysiCell**
- Simulation & Analysis

Config Basics

- Domain size
 - $X = [-500, 500]$
 - $Y = [-500, 500]$
 - $Z = [-10, 10]$
 - $dx, dy, dz = 20$
 - $Use_2D = true$
- Max-time = 1440 min
- Thread = your choice
- Save data :
SVG = 30 min,



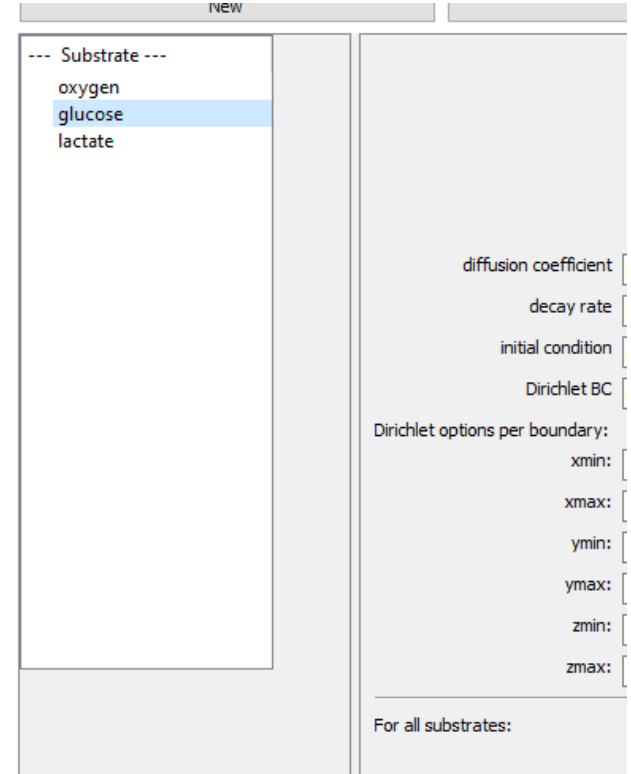
The screenshot shows the PhysiCell Studio configuration window with the following settings:

- Domain (micron):**
 - Xmin: -500, Xmax: 500, dx: 20
 - Ymin: -500, Ymax: 500, dy: 20
 - Zmin: -10, Zmax: 10, dz: 20
- Times:**
 - Max Time: 1440 min (with a "+ 1 day" button)
 - Diffusion dt: 0.01 min
 - Mechanics dt: 0.1 min
 - Phenotype dt: 6 min
- Misc runtime parameters:**
 - # threads: 10
 - output folder: output
 - Save data (intervals):
 - ☒ SVG, 30 min
 - ☒ Full, 30 min
 - ☒ Sync
- Initial conditions of cells (x,y,z, type):**
 - ☐ enable, folder: ./config, file: cells.csv, Import button
- Cells' global behaviors:**
 - ☒ virtual walls
 - ☐ disable springs

Full = 30 min

Microenvironment

- Microenvironment Tab
- Let's add “oxygen”, “glucose”, “lactate”



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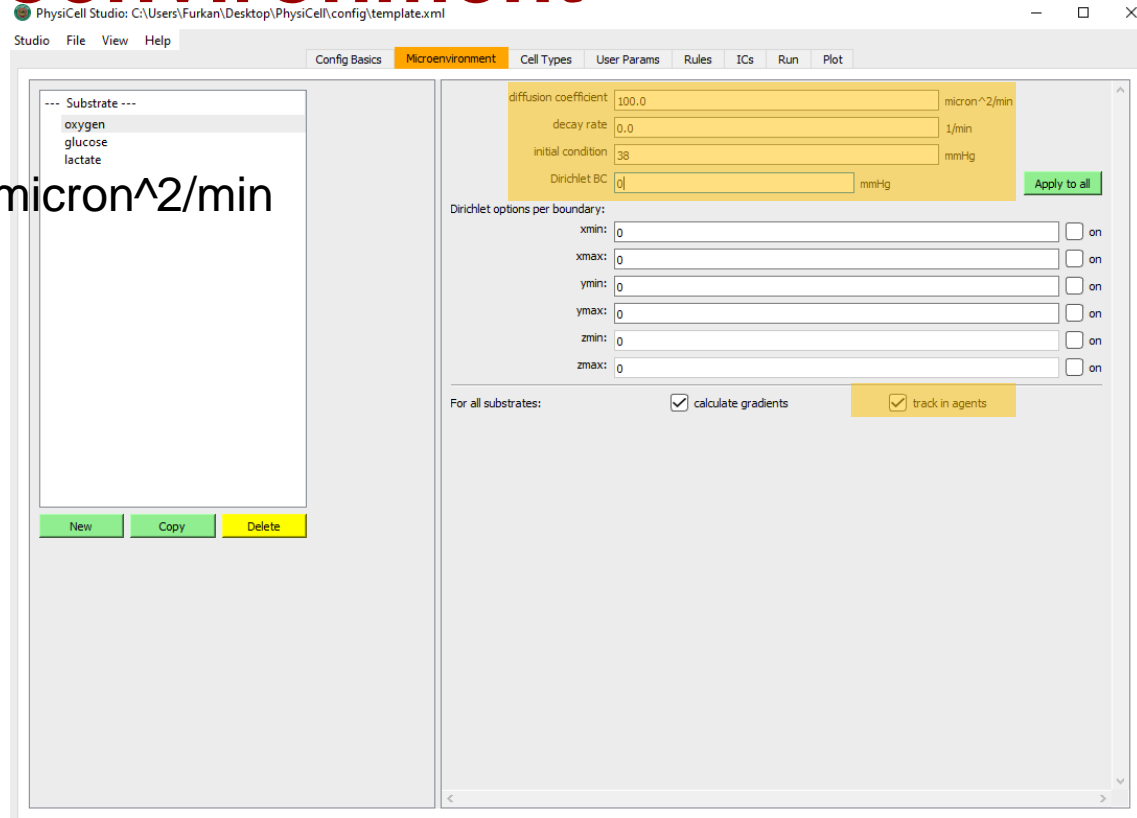
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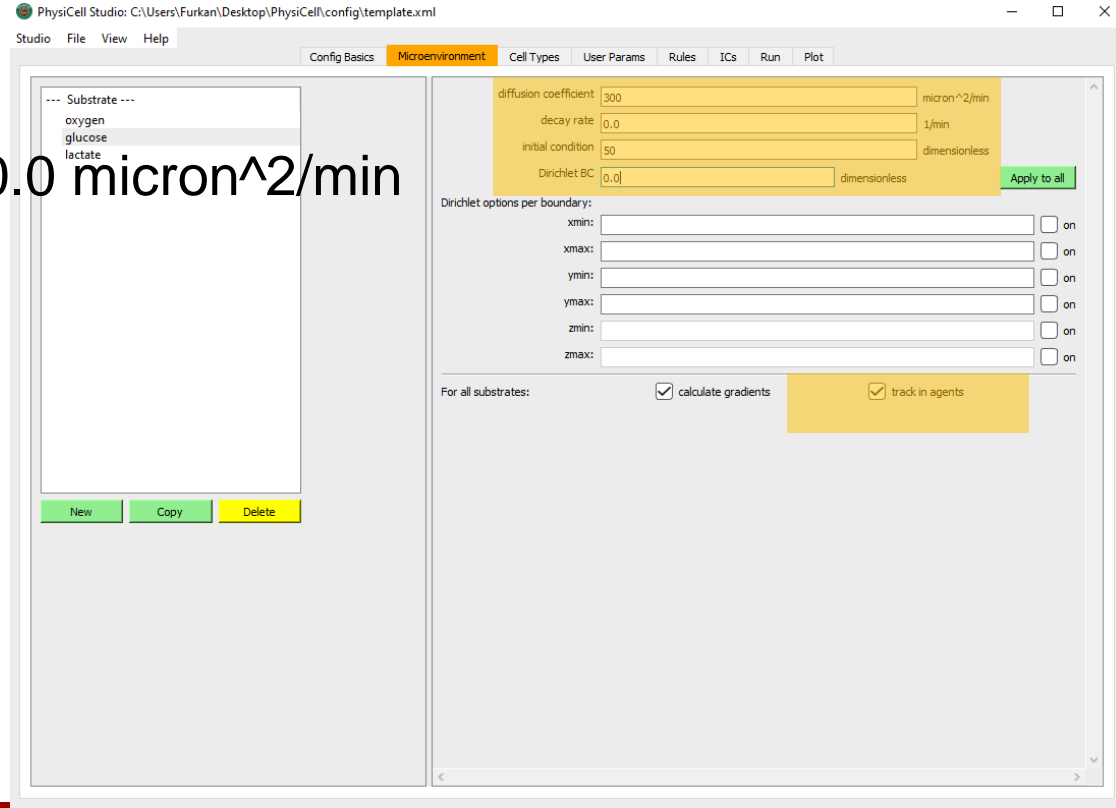
Microenvironment

- Oxygen
- Diffusion Coefficient = $100.0 \text{ micron}^2/\text{min}$
- Decay Rate = 0.0 1/min
- Initial condition = 38.0 mmHg
- Dirichlet = OFF
- Track in agents = ON



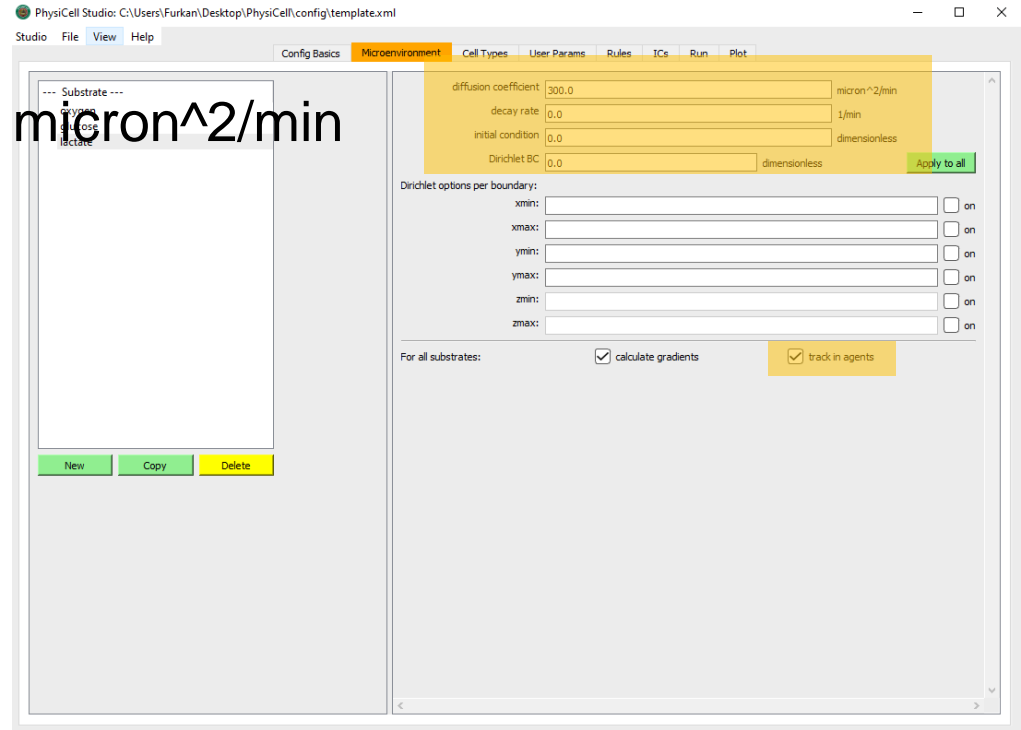
Microenvironment

- Glucose
- Diffusion Coefficient = $300.0 \text{ micron}^2/\text{min}$
- Decay Rate = 0.0 1/min
- Initial condition = 50.0 a.u
- Dirichlet = OFF
- Track in agents = ON



Microenvironment

- Lactate
- Diffusion Coefficient = 300.0 $\mu\text{m}^2/\text{min}$
- Decay Rate = 0.0 1/min
- Initial condition = 0.0 mmHg
- Dirichlet = OFF
- Track in agents = ON



Cell Type

- Only one type of cell in the name of “default”
- Cycle
 - Live Cells
 - Transition rate(s)
 - 0.0

The screenshot displays the 'Cell Types' configuration window in the PhysiCell software. The 'Cycle' sub-tab is selected, showing options for 'transition rate(s)' (selected) and 'duration(s)'. A dropdown menu is set to 'live cells'. The 'phase 0->0 transition rate' is set to '0.0' with a 'Fixed' checkbox. The unit '1/min' is indicated on the right.

Config Basics	Microenvironment	Cell Types	User Params	Rules	ICs	Run	Plot
<div><div>Cycle</div><div>Death Volume Mechanics Motility Secretion Interactions Intracellular Custom Data</div><div><div><input checked="" type="radio"/> transition rate(s) <input type="radio"/> duration(s)</div><div>live cells</div><div>phase 0->0 transition rate <input type="text" value="0.0"/> <input type="checkbox"/> Fixed</div></div><div>1/min</div></div>							

Cell Type

- No Death

Cycle **Death** Volume Mechanics Motility Secretion Interactions Intracellular Custom Data

Apoptosis

death rate 1/min

☒ transition rate ☐ duration

phase 0->1 transition rate ☒ Fixed 1/min

phase 0 duration ☒ Fixed min

unlysed fluid change rate 1/min

lysed fluid change rate 1/min

cytoplasmic biomass change rate 1/min

nuclear biomass change rate 1/min

calcification rate 1/min

relative rupture volume

Necrosis

death rate 1/min

☒ transition rate ☐ duration

phase 0->1 transition rate ☒ Fixed 1/min

phase 1->2 transition rate ☒ Fixed 1/min

phase 0 duration ☒ Fixed min

phase 1 duration ☒ Fixed min

Cell Type

- No change in the Volume and Mechanics Tab

PhysiCell Model Builder: C:\Users\Furkan\Documents\GitHub\PhysiCell-model-builder\data\template.xml

File Config Basics Microenvironment **Cell Types** User Params

New Copy Delete

Cell Type --- default

	Cycle	Death	Volume	Mechanics	Motility	Secretion	Interactions	Intracellular	Custom Data
total	2494								micron ³
fluid fraction	0.75								
nuclear	540								micron ³
fluid change rate	0.05								1/min
cytoplasmic biomass change rate	0.0045								1/min
nuclear biomass change rate	0.0055								1/min
calcification fraction	0								
calcified rate	0								1/min
relative rupture volume	2.0								

PhysiCell Model Builder: C:\Users\Furkan\Documents\GitHub\PhysiCell-model-builder\data\template.xml

File Config Basics Microenvironment **Cell Types** User Params

New Copy Delete

Cell Type --- default

	Cycle	Death	Volume	Mechanics	Motility	Secretion	Interactions	Intracellular	Custom Data
cell-cell adhesion strength	0.4								micron/min
cell-cell repulsion strength	10.0								micron/min
cell-EM adhesion strength	4.0								micron/min
cell-EM repulsion strength	10.0								micron/min
relative max adhesion distance	1.25								
cell adhesion affinity	default								1.0
Options:									
relative equilibrium distance	1.8							<input type="checkbox"/> enable	
absolute equilibrium distance	15.12							<input type="checkbox"/> enable	micron
elastic constant	0.01								1/min
attachment rate	10.0								1/min
detachment rate	0.0								1/min

Cell Type

- Motility
- Speed = 0.0
- Persistence Time = 0.1
- Migration Bias = 0.9
- Enable-motility
- 2D = Yes

The screenshot shows the 'Cell Types' configuration window in PhysiCell. The 'Motility' sub-tab is active, displaying the following settings:

- speed:** 0.0 (micron/min)
- persistence time:** 0.1 (min)
- migration bias:** .9
- enable motility:** ☐ (unchecked)
- 2D:** ☒ (checked)
- Chemotaxis:** ☐ enabled (unchecked)
 - Dropdown: oxygen
 - Direction: ☒ towards, ☐ against
- Advanced Chemotaxis:** ☐ enabled (unchecked)
 - Dropdown: oxygen
 - Sensitivity: 0.0 (slider)
 - ☐ normalize gradient (unchecked)
- Reset to PhysiCell defaults:** (button)

Cell Type : Secretion

- Oxygen Tab
- Uptake rate = 0.005

The screenshot shows the PhysiCell configuration window with the 'Cell Types' tab selected. Within this tab, the 'Secretion' sub-tab is active. A dropdown menu shows 'oxygen' as the selected substance. Below this, four parameters are listed with input fields and units:

Parameter	Value	Unit
secretion rate	0	1/min
target	1	sub. density
uptake rate	0.005	1/min
net export rate	0	total/min

A yellow button labeled 'Reset to PhysiCell defaults' is located at the bottom of the configuration area.

Cell Type : Secretion

- Glucose Tab
- Uptake rate = 0.001

The screenshot displays the 'Secretion' configuration window for a 'glucose' cell type. The window features a tabbed interface with 'Secretion' selected. Below the tabs, a dropdown menu shows 'glucose'. Four parameters are listed with input fields and units: 'secretion rate' (0.0, 1/min), 'target' (0.0, sub. density), 'uptake rate' (0.001, 1/min), and 'net export rate' (0.0, total/min). The 'uptake rate' row is highlighted in yellow. A yellow button labeled 'Reset to PhysiCell defaults' is located at the bottom left.

Parameter	Value	Unit
secretion rate	0.0	1/min
target	0.0	sub. density
uptake rate	0.001	1/min
net export rate	0.0	total/min



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Cell Type : Secretion

- Lactate Tab
- Secretion Target = 10.0

The screenshot displays the 'Secretion' configuration window for a 'lactate' cell type. The window has a tabbed interface with 'Secretion' selected. Below the tabs, a dropdown menu shows 'lactate'. Four parameters are listed with input fields and units:

Parameter	Value	Unit
secretion rate	0.0	1/min
target	10.0	sub. density
uptake rate	0.0	1/min
net export rate	0.0	total/min

A yellow button labeled 'Reset to PhysiCell defaults' is located at the bottom left of the configuration area.

Cell Type

- No Interactions

Cycle	Death	Volume	Mechanics	Motility	Secretion	Interactions	Intracellular	Custom Data
dead phagocytosis rate		<input type="text" value="0"/>		1/min				
live phagocytosis rate	<input type="text" value="default"/>	<input type="text" value="0"/>	1/min					
attack rate	<input type="text" value="default"/>	<input type="text" value="0"/>	1/min					
damage rate		<input type="text" value="1"/>		1/min				
fusion rate	<input type="text" value="default"/>	<input type="text" value="0"/>	1/min					
transformation rate	<input type="text" value="default"/>	<input type="text" value="0"/>	1/min					
Reset to PhysiCell defaults								

Cell Custom Data

- We need to create intracellular data to save the data
- $\text{intra_oxy} = 0.0$
- $\text{intra_glu} = 0.0$
- $\text{intra_lac} = 0.0$
- $\text{intra_energy} = 0.0$

Cycle		Death		Volume		Mechanics		Motility		Secretion		Inte	
<div>Search for Name...</div>													
	Name	Value	Conserve	Units									
1	intra_oxy	0.0	<input type="checkbox"/>	dimensionless									
2	intra_glu	0.0	<input type="checkbox"/>										
3	intra_lac	0.0	<input type="checkbox"/>										
4	intra_energy	0.0	<input type="checkbox"/>										
5		0.0	<input type="checkbox"/>										
6		0.0	<input type="checkbox"/>										
7		0.0	<input type="checkbox"/>										



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User Params

- initial_internal_oxygen (double) = 0.8
- initial_internal_glucose (double) = 15
- initial_internal_lactate (double) = 0.0
- initial_energy (double) =450

	Name	Type	Value	Units	Desc
1	random_seed	int ▼	0	dimensionless	
2	initial_internal_oxygen	double ▼	0.8	none	(for each cell type)
3	initial_internal_glucose	double ▼	15		
4	initial_internal_lactate	double ▼	0.0		
5	initial_energy	double ▼	450		
6		double ▼			
7		double ▼			

Save

- Let's check is it right

Let's add intracellular attribute at config

```
<intracellular type="roadrunner">  
  
<sbml_filename>./config/Toy_Metabolic_Model.xml</sbml_filename>  
  <intracellular_dt>0.01</intracellular_dt>  
  <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>  
</intracellular>
```

Reproducing

- We will remove intracellular-related parts
- And build one-by-one
- At custom.cpp
 - setup_tissue():
 - ♦ Remove lines between #174-198
 - update_intracellular():
 - ♦ Remove anything in if loop #216-245
 - » Beware line numbers might shift after first removal

----- GROUND_ZERO.zip -----

setup_tissue(): after cell seeding

```
// 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:intra_glu" , parameters.doubles("initial_internal_glucose"));
set_single_behavior( pCell , "custom:intra_lac" , parameters.doubles("initial_internal_lactate"));
set_single_behavior( pCell , "custom:intra_energy" , parameters.doubles("initial_energy"));

double cell_volume = pCell->phenotype.volume.total;

// set the internalized values

set_single_behavior( pCell , "custom:intra_oxy" , parameters.doubles("initial_internal_oxygen"));

pCell->phenotype.molecular.internalized_total_substrates[oxygen_substrate_index]= get_single_signal( pCell,
"custom:intra_oxy") * cell_volume;

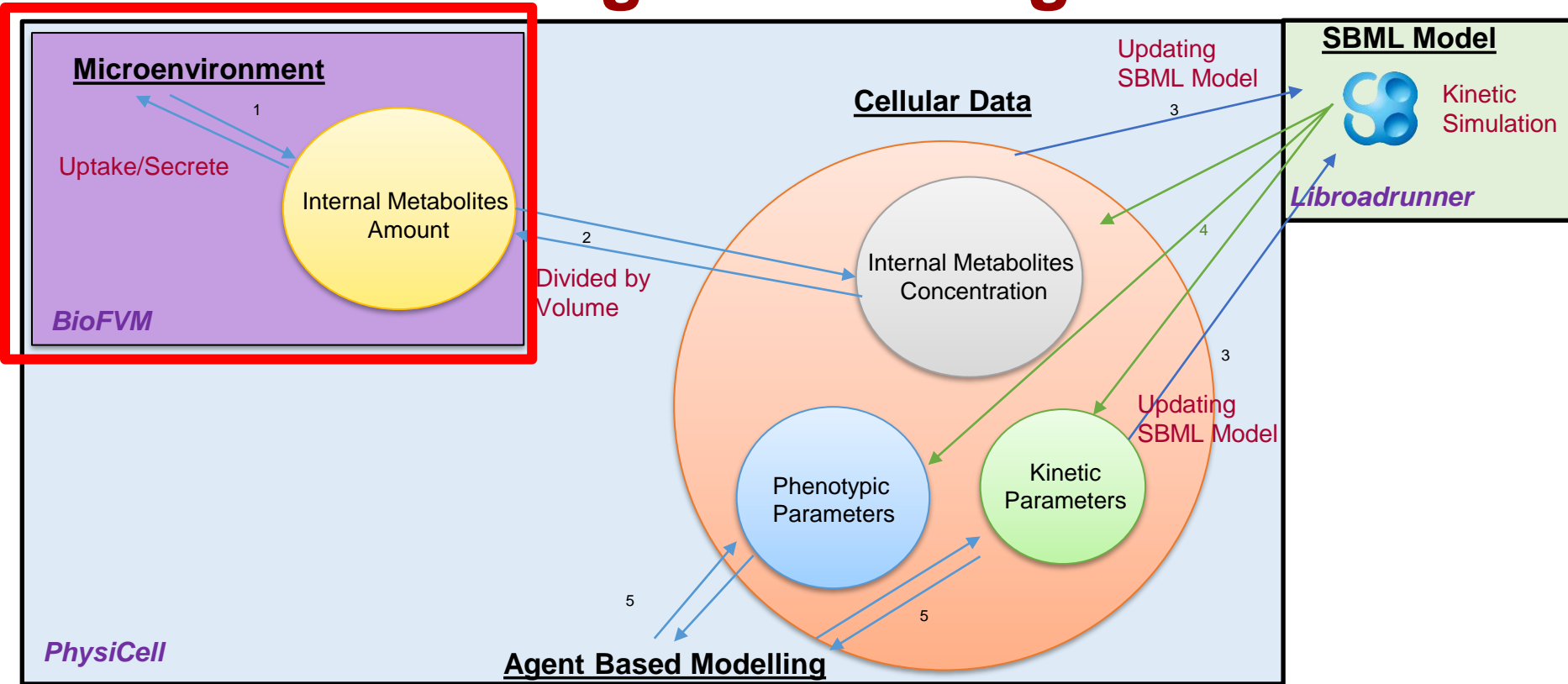
pCell->phenotype.molecular.internalized_total_substrates[glucose_substrate_index]= get_single_signal( pCell,
"custom:intra_glu") * cell_volume;

pCell->phenotype.molecular.internalized_total_substrates[lactate_substrate_index]= get_single_signal( pCell,
"custom:intra_lac") * cell_volume;

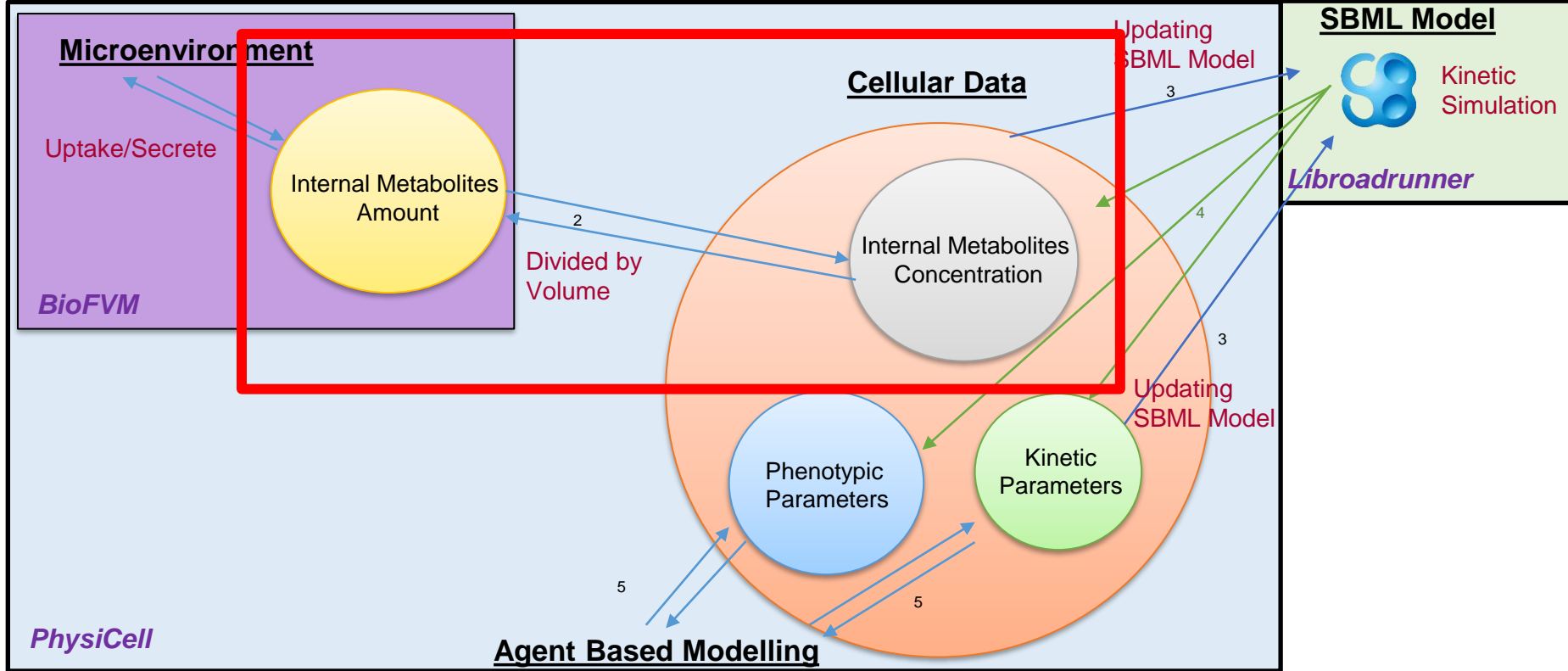
pCell->phenotype.intracellular->start();

pCell->phenotype.intracellular->set_parameter_value("Energy",get_single_signal( pCell, "custom:intra_energy"));
```

Integration Design



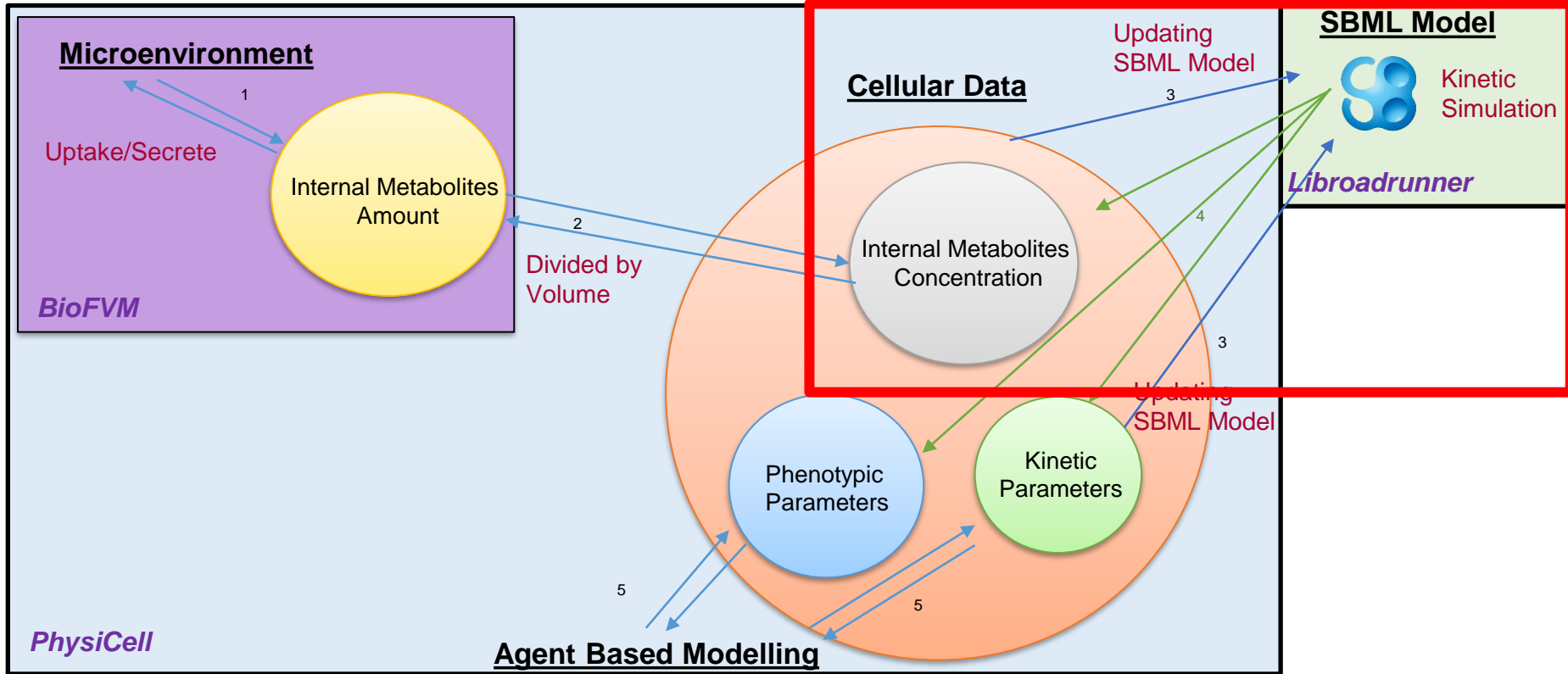
Integration Design



Let's fill update_intracellular

```
// Cell Volume  
  
double cell_volume = (*all_cells)[i]->phenotype.volume.total;  
  
// Get Intracellular Concentrations  
  
double oxy_val_int = get_single_signal((*all_cells)[i], "intracellular oxygen");  
double glu_val_int = get_single_signal((*all_cells)[i], "intracellular glucose");  
double lac_val_int = get_single_signal((*all_cells)[i], "intracellular lactate");
```

Integration Design



Let's fill update_intracellular

```
// 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);
```



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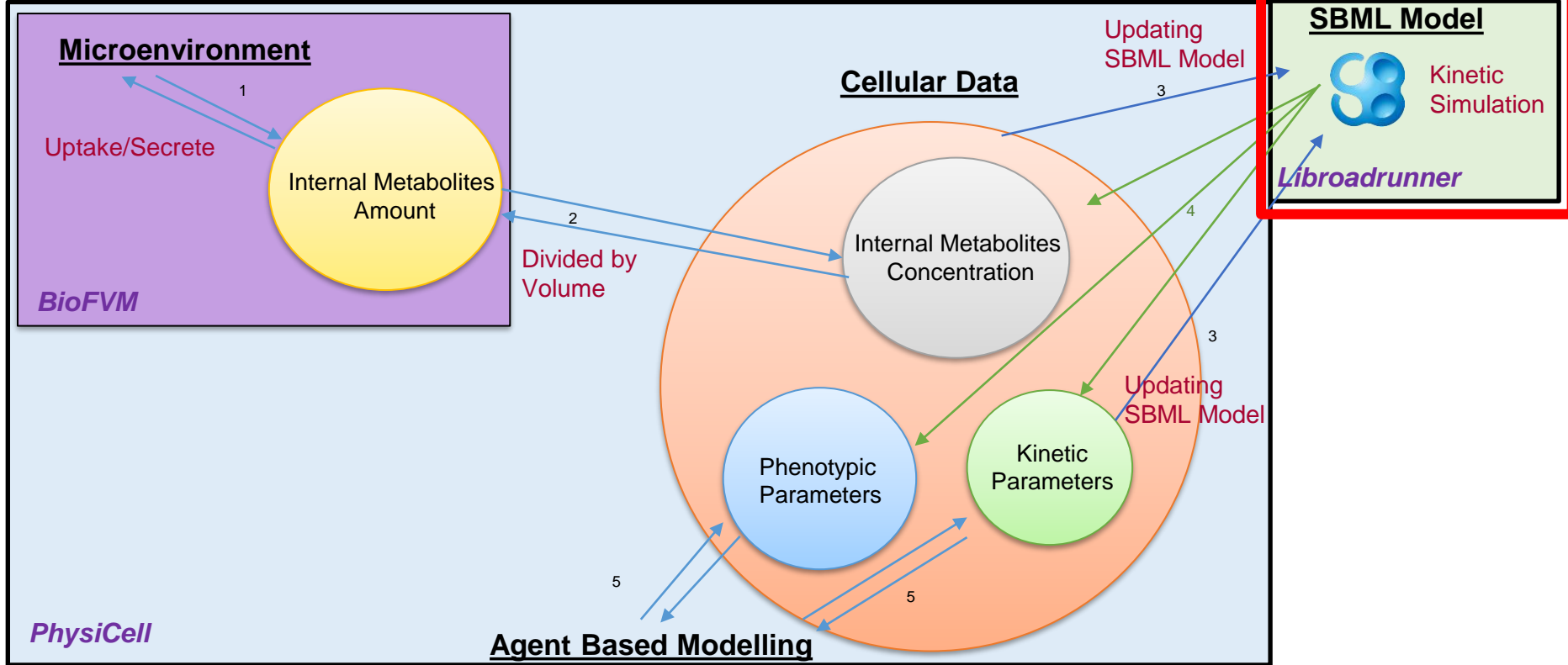
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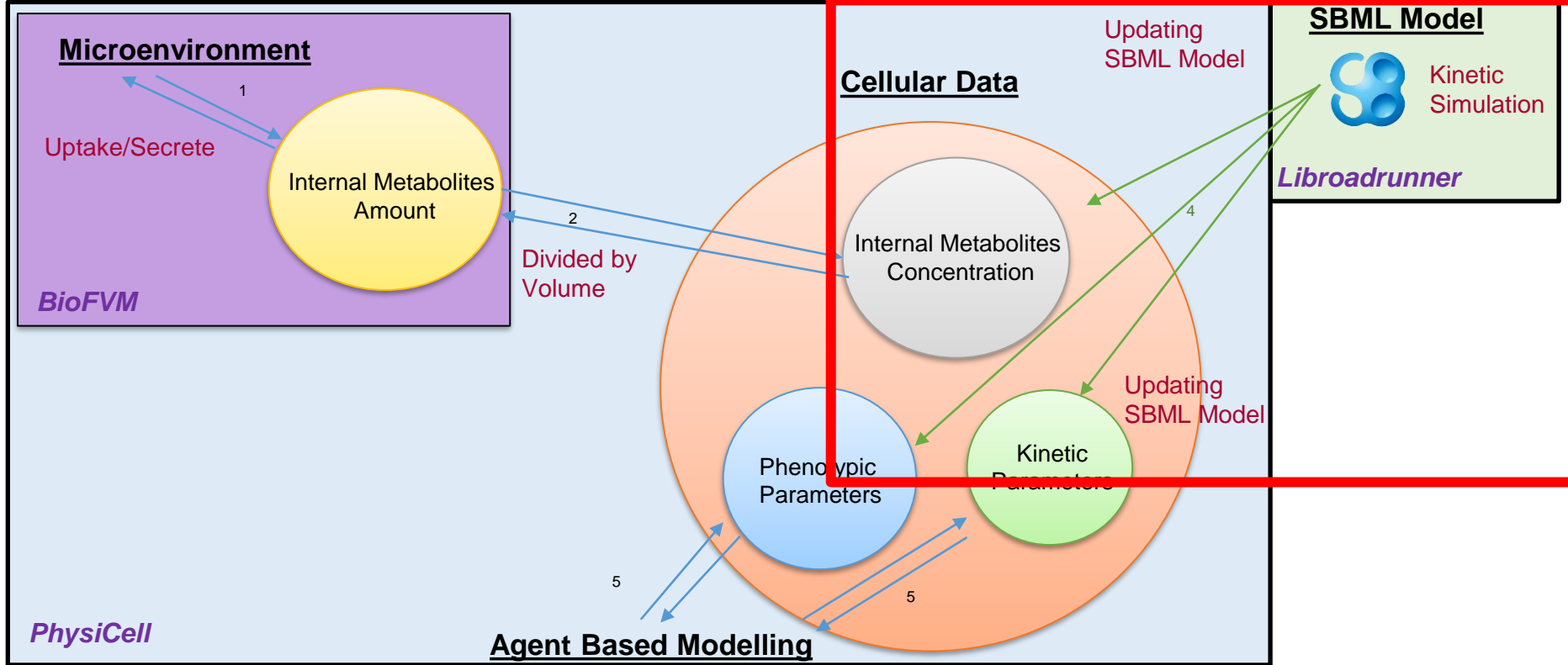
Integration Design



Let's fill update_intracellular

```
// SBML Simulation
(*all_cells)[i]->phenotype.intracellular->update();
// Phenotype Simulation
(*all_cells)[i]->phenotype.intracellular->update_phenotype_parameters((*all_cells)[i])
```

Integration Design



Let's fill update_intracellular

```
// 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

set_single_behavior( (*all_cells)[i] , "custom:intra_oxy" , (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Oxygen") );

set_single_behavior( (*all_cells)[i] , "custom:intra_glu" , (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Glucose") );

set_single_behavior( (*all_cells)[i] , "custom:intra_lac" , (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Lactate") );

set_single_behavior( (*all_cells)[i] , "custom:intra_energy" , (*all_cells)[i]->phenotype.intracellular->get_parameter_value("Energy") );
```

Let's Simulate

- I will use `beta/plot_cells.py` and `beta/plot_data` for analysis

```
(base) C:\Users\Furkan\Desktop\PhysiCell>python beta/plot_data.py
```

----- Final_Model.zip -----



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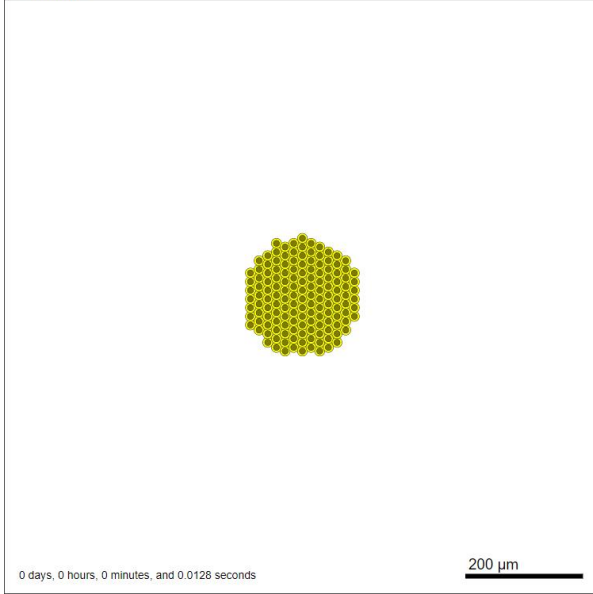
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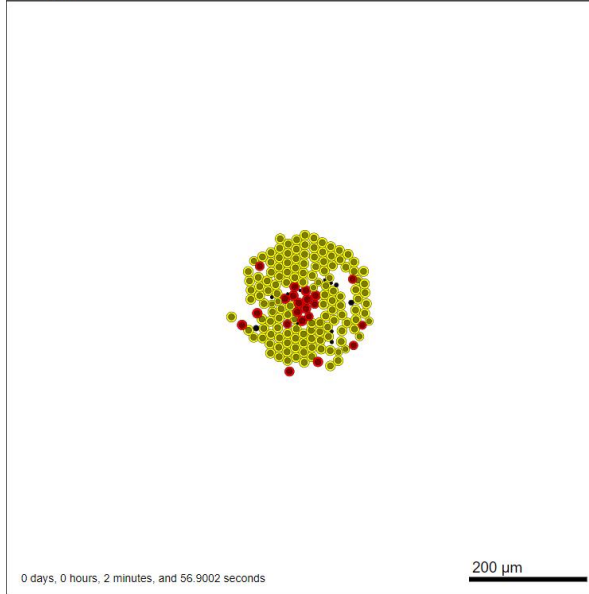
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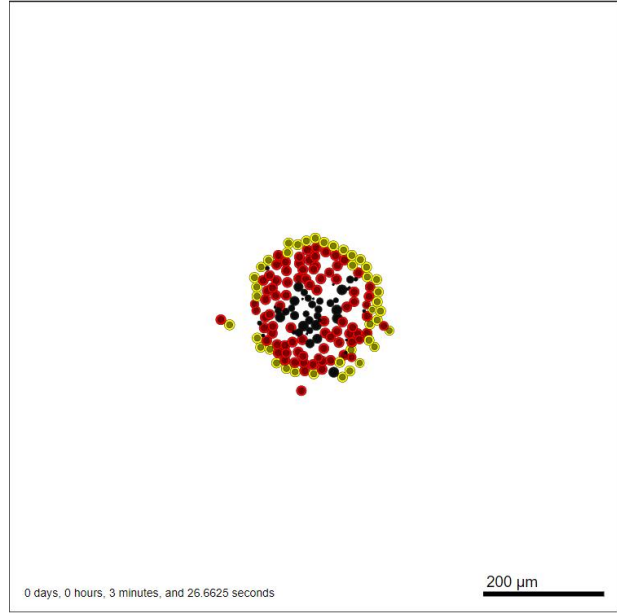
Current time: 0 days, 0 hours, and 0.00 minutes, $z = 0.00 \mu\text{m}$
144 agents



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



If time allows

- Let's change `dt_intracellular` to 6 min
- Do you see any differences?

Up next

- End of live sessions for today.
- One lecture is left tomorrow at 11:05am (ET)
- Let's meet at the Hackathon for the Team Time

Funding Acknowledgements



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The Common
Fund



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PhysiCell Development:

- Breast Cancer Research Foundation
- Jayne Koskinas Ted Giovanis Foundation for Health and Policy
- National Cancer Institute (U01CA232137)
- National Science Foundation (1720625, 1818187)

Training Materials:

- Administrative supplement to NCI U01CA232137 (Year 5)

Other Funding:

- NCI / DOE / Frederick National Lab for Cancer Research (21X126F)
- DOD / Defense Threat Reduction Agency (HDTRA12110015)
- NIH Common Fund (3OT2OD026671-01S4)