

Slides, videos, links and more:

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

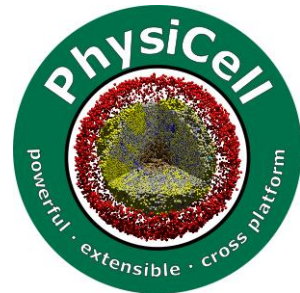
Advanced Session 7: Intracellular with libRoadrunner (interactive demo)

Furkan Kurtoglu

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

PhysiCell Project

August 2023



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

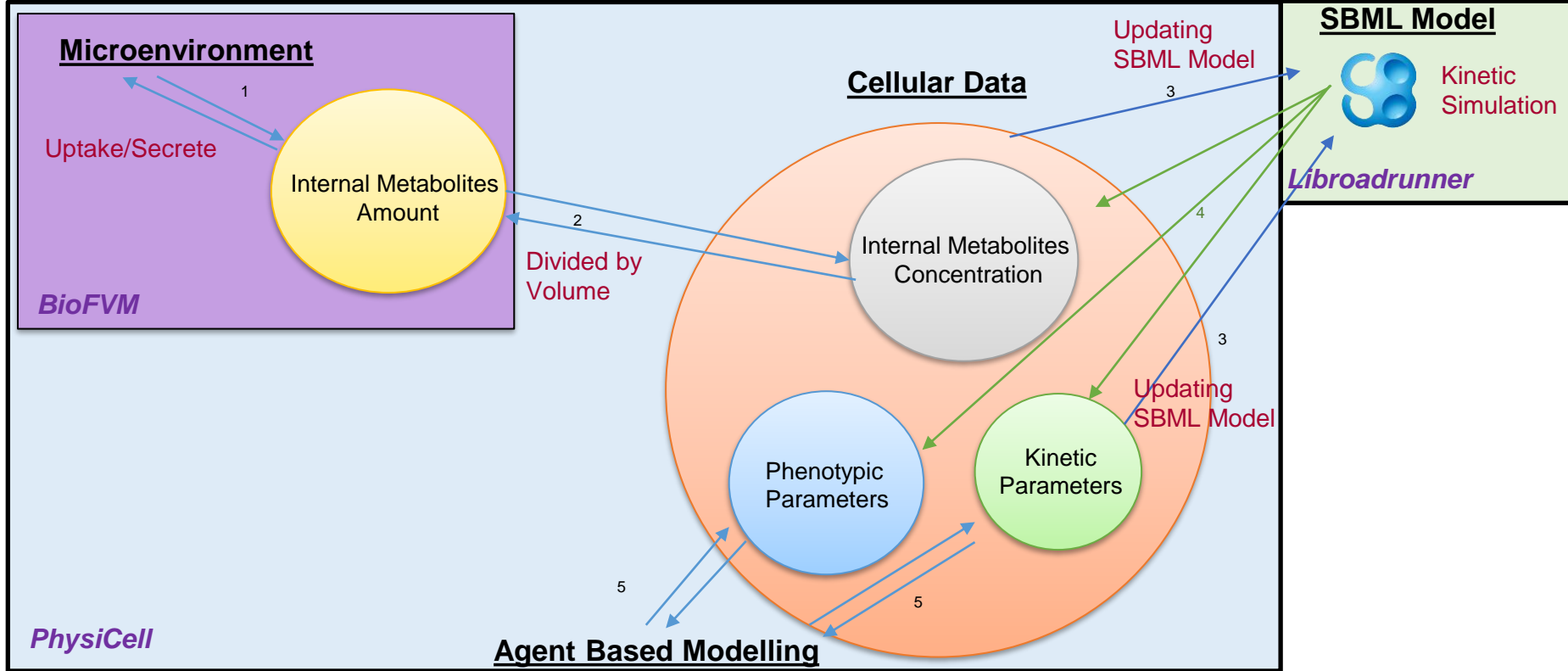
Agenda:

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

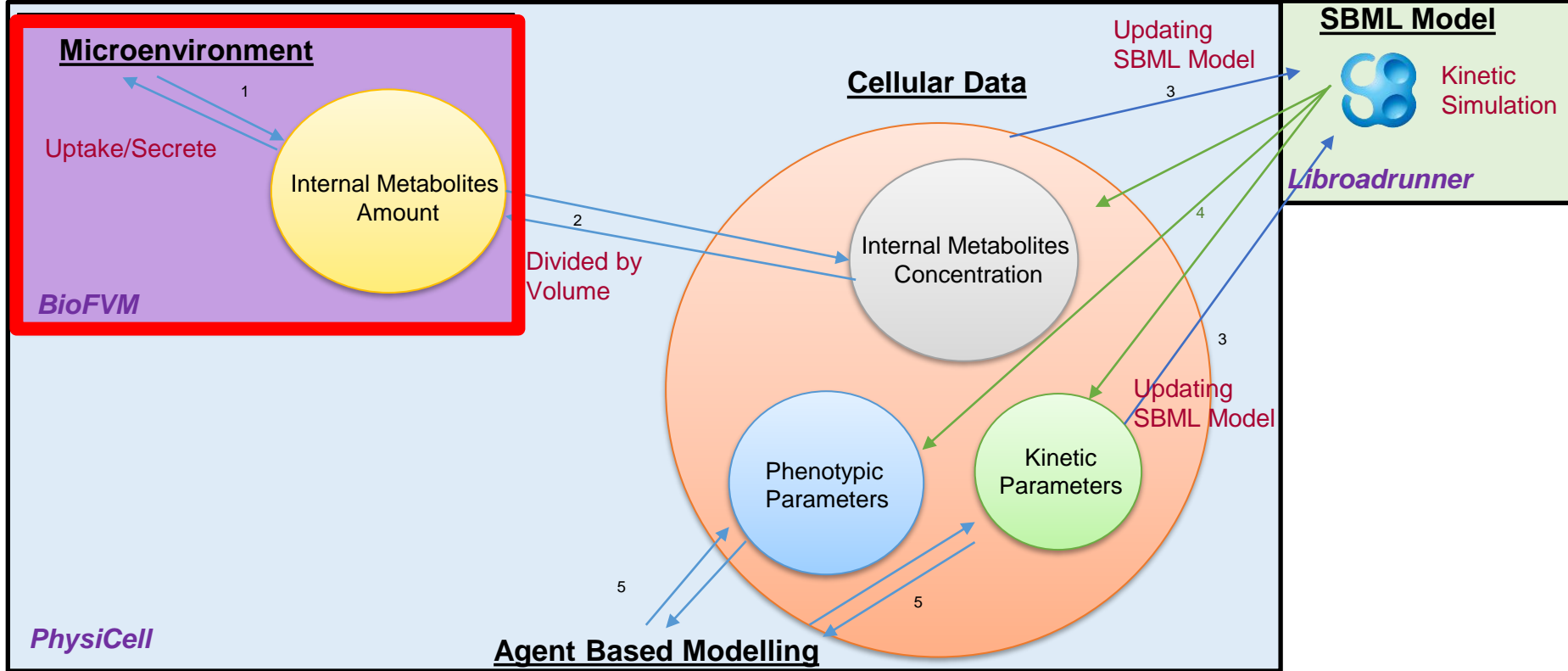
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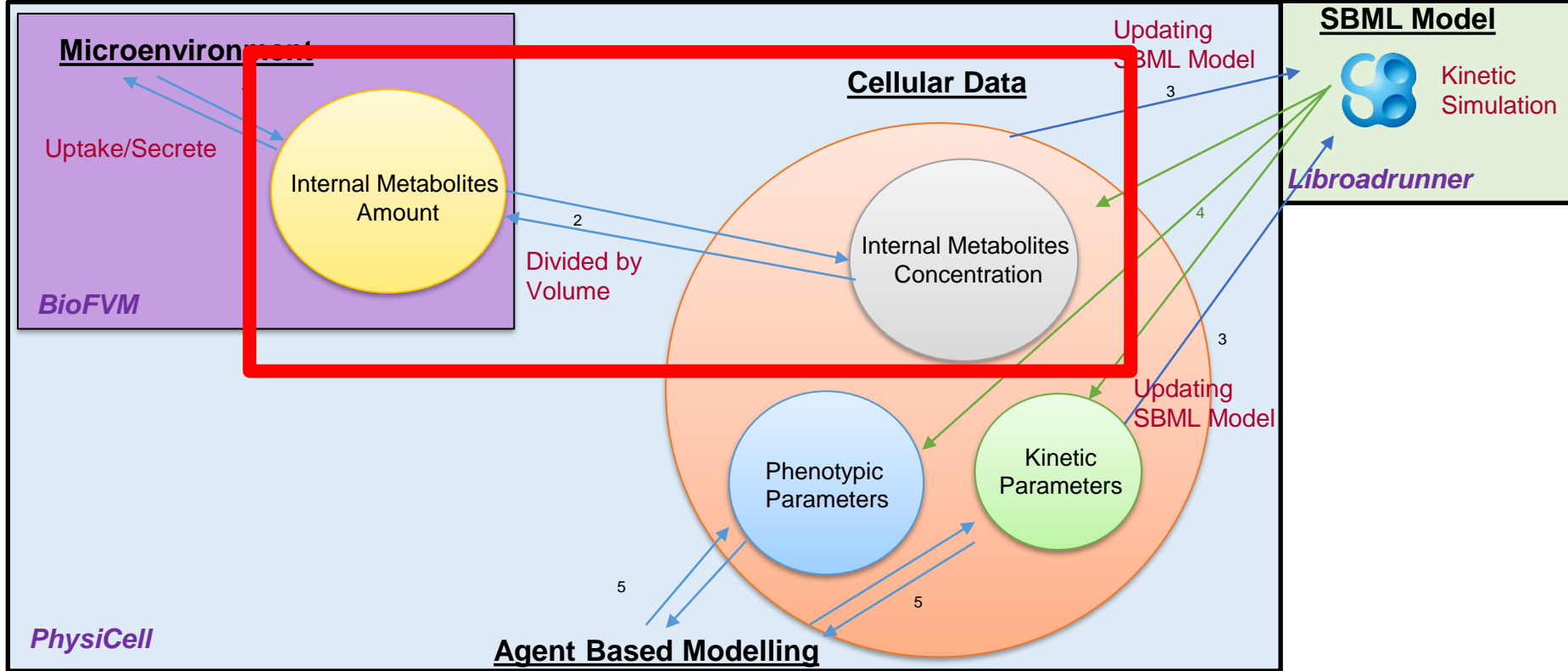
Integration Design



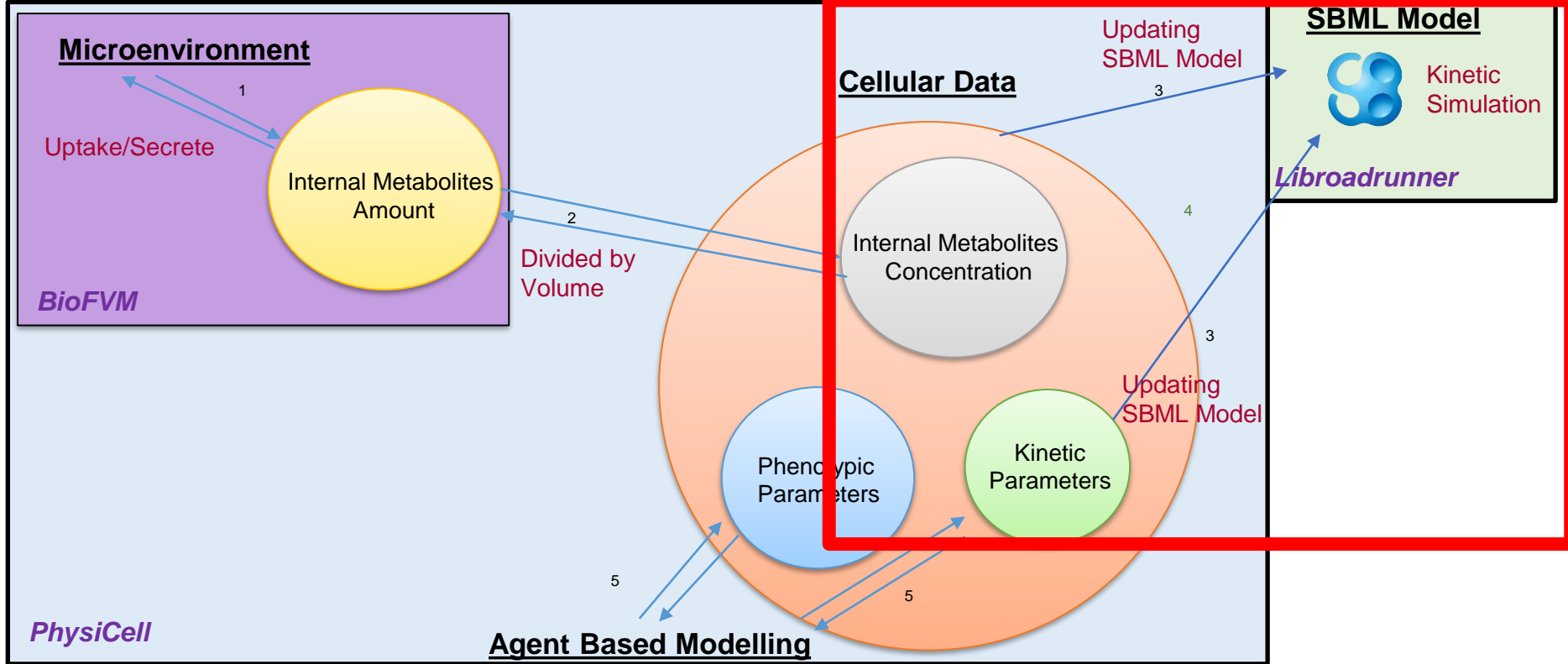
Integration Design



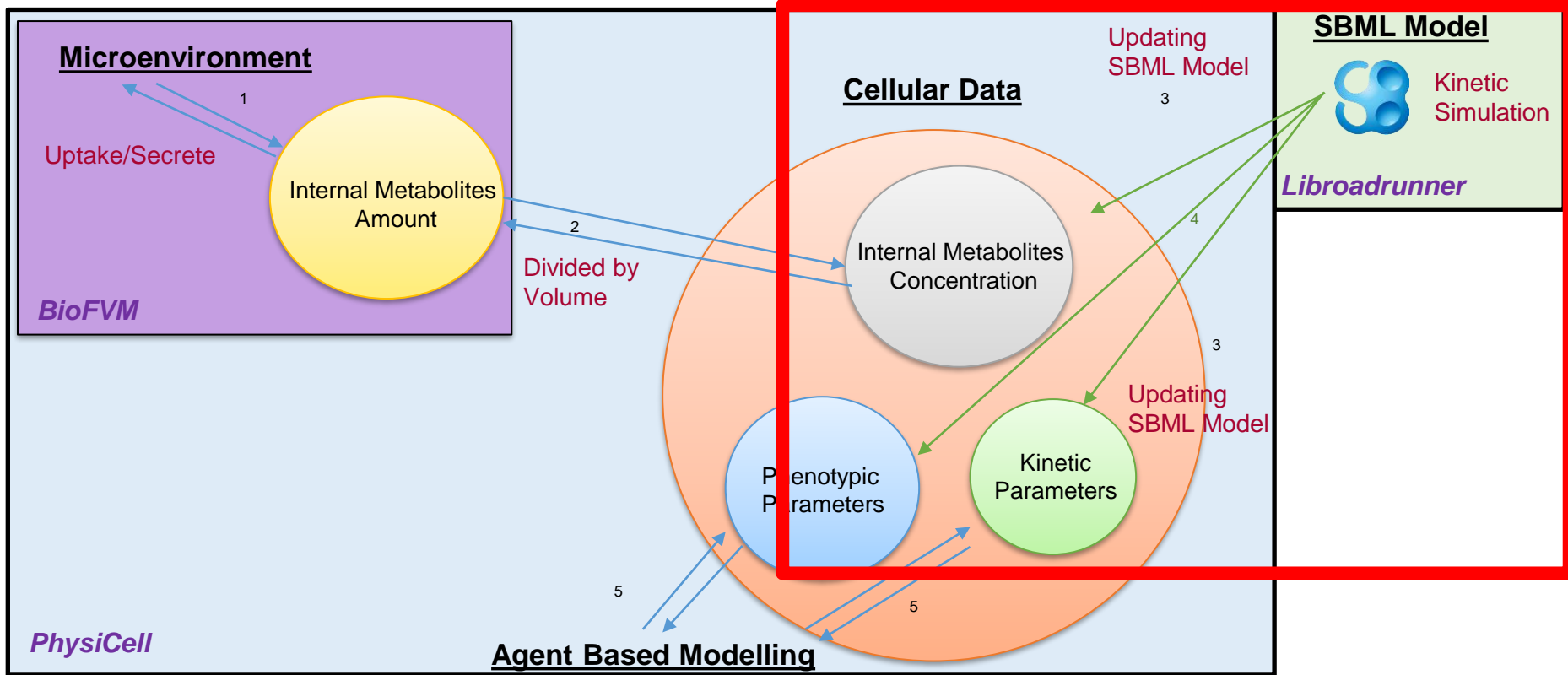
Integration Design



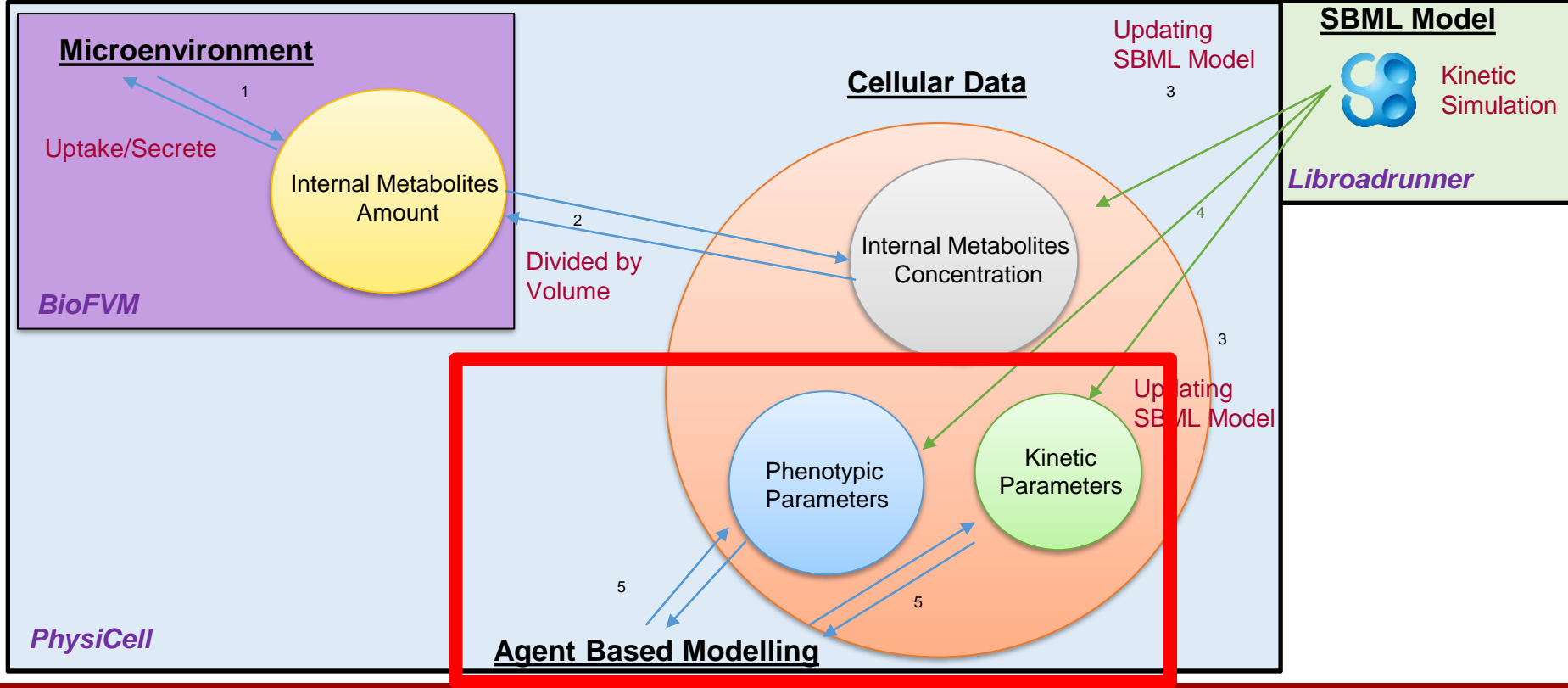
Integration Design



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

Agenda:

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SBML Exploration



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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 (with an "Import" button)
- Cells' global behaviors:**
 - ☒ virtual walls
 - ☐ disable springs

Full = 30 min

Microenvironment

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

NEW

--- Substrate ---

- oxygen
- glucose
- lactate

diffusion coefficient [

decay rate [

initial condition [

Dirichlet BC [

Dirichlet options per boundary:

xmin: [

xmax: [

ymin: [

ymax: [

zmin: [

zmax: [

For all substrates:



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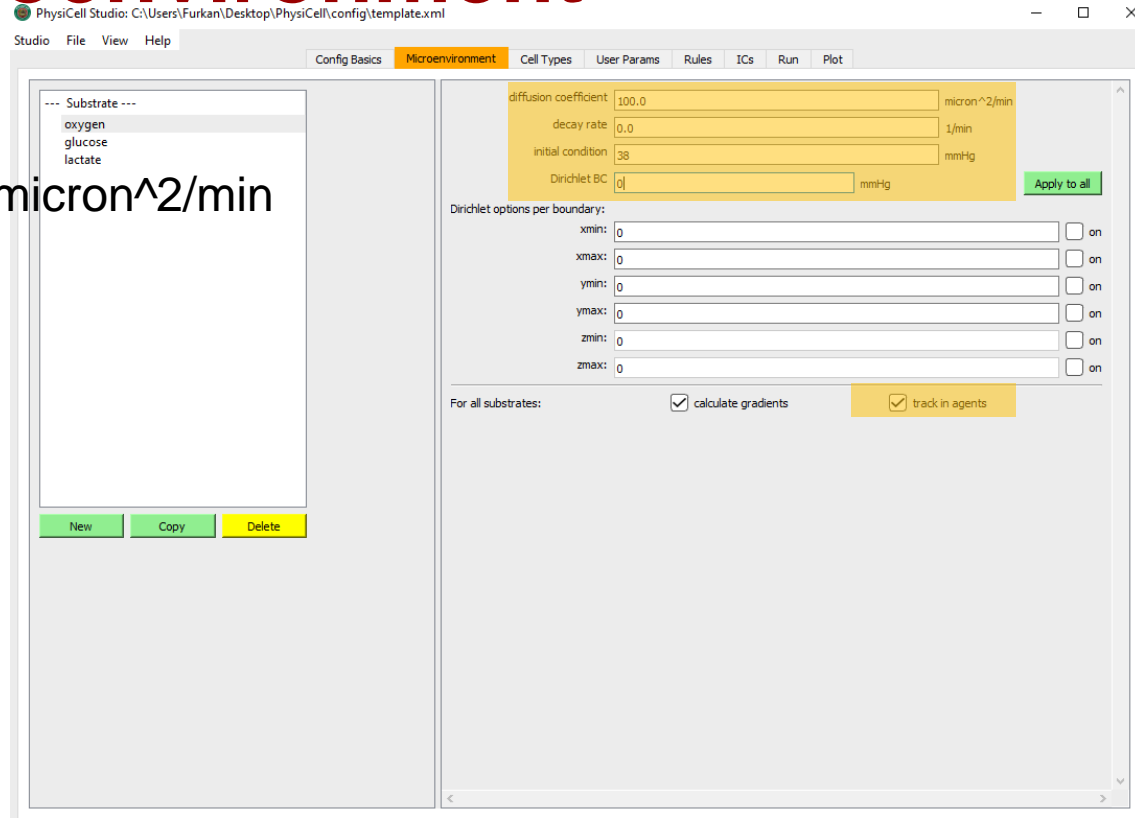
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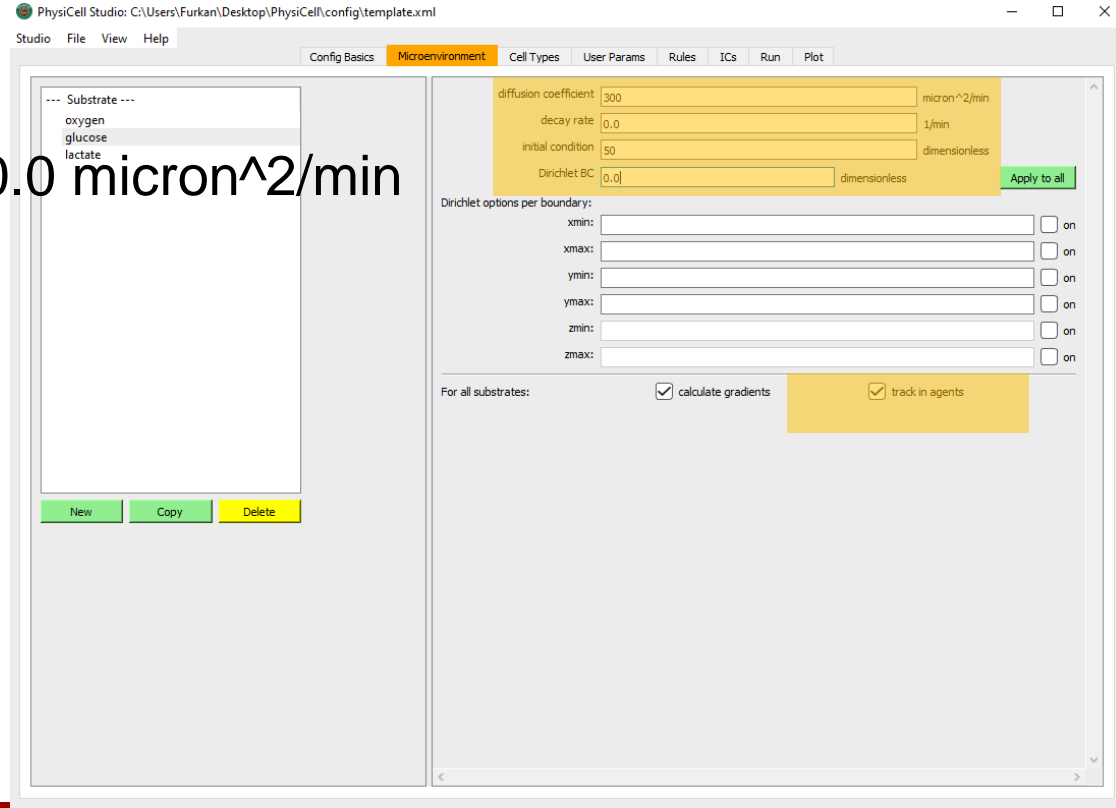
Microenvironment

- 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



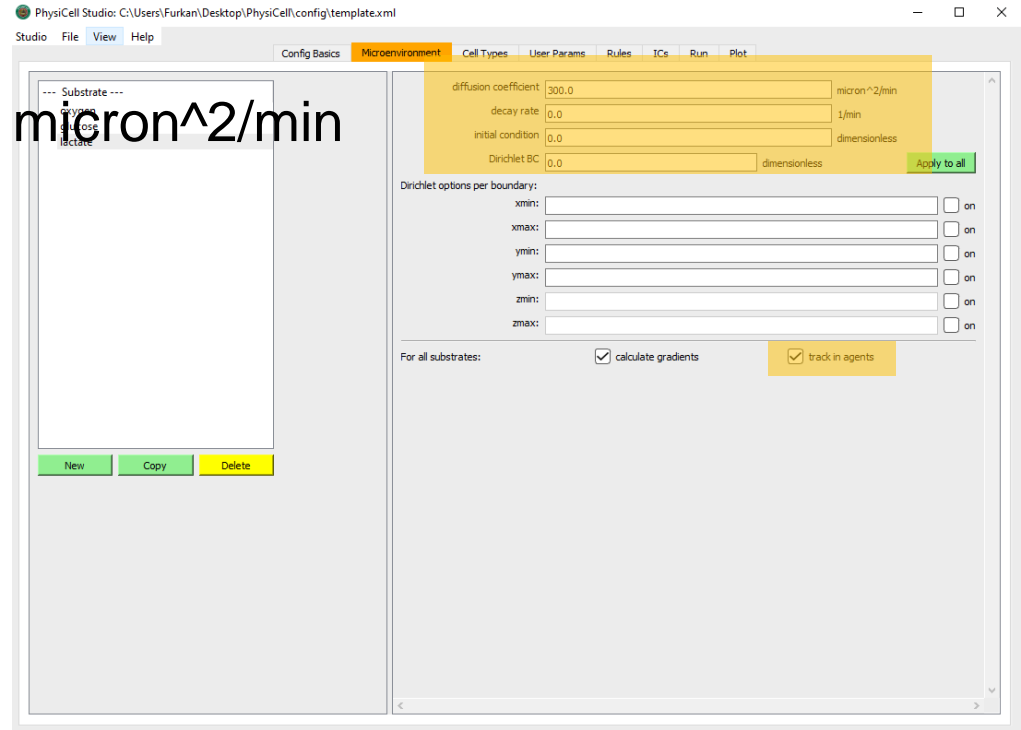
Microenvironment

- 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



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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 top navigation bar includes tabs for 'Config Basics', 'Microenvironment', 'Cell Types' (which is selected), 'User Params', 'Rules', 'ICs', 'Run', and 'Plot'. Within the 'Cell Types' tab, there are sub-tabs for 'Cycle', 'Death', 'Volume', 'Mechanics', 'Motility', 'Secretion', 'Interactions', 'Intracellular', and 'Custom Data'. The 'Cycle' sub-tab is active, showing two radio buttons: 'transition rate(s)' (selected) and 'duration(s)'. Below these is a dropdown menu currently set to 'live cells'. A text input field for 'phase 0->0 transition rate' contains the value '0.0', with a 'Fixed' checkbox to its right. On the far right of the panel, a unit indicator shows '1/min'.

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)
- Chemotaxis target:** oxygen (selected from dropdown)
- Chemotaxis direction:** ☒ towards, ☐ against
- Advanced Chemotaxis:** ☐ enabled (unchecked)
- Advanced Chemotaxis target:** oxygen (selected from dropdown)
- 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 'Cell Types' configuration window in PhysiCell, specifically the 'Secretion' tab. A dropdown menu is set to 'oxygen'. The following parameters are configured:

Parameter	Value	Unit / Description
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 panel.

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 the 'lactate' cell type. The window has a tabbed interface with 'Secretion' selected. Below the tabs, a dropdown menu shows 'lactate'. The configuration parameters are as follows:

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
<button>Reset to PhysiCell defaults</button>								

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	
Search for Name...													
	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



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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;

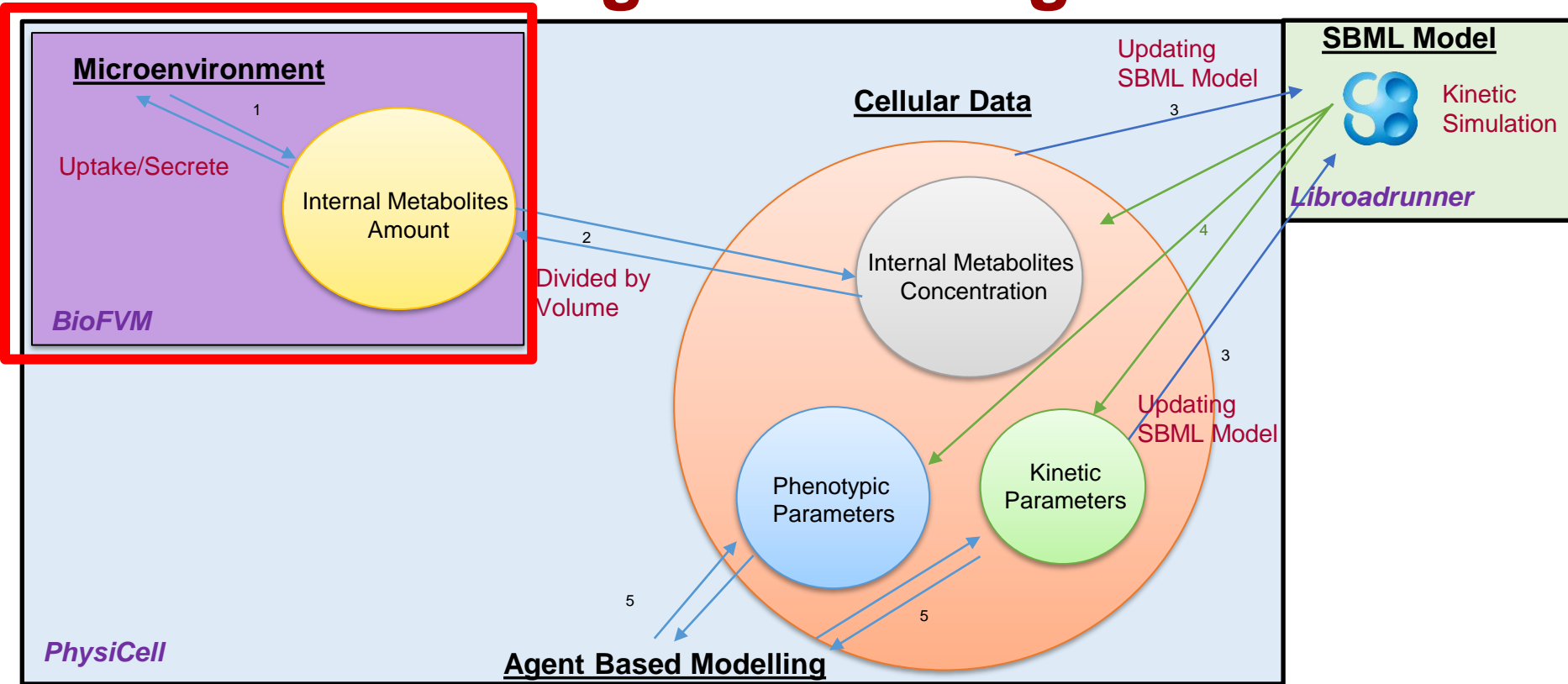
pCell->phenotype.molecular.internalized_total_substrates[glucose_substrate_index]= get_single_signal( pCell,
"custom:intra_glu") * cell_volume;

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

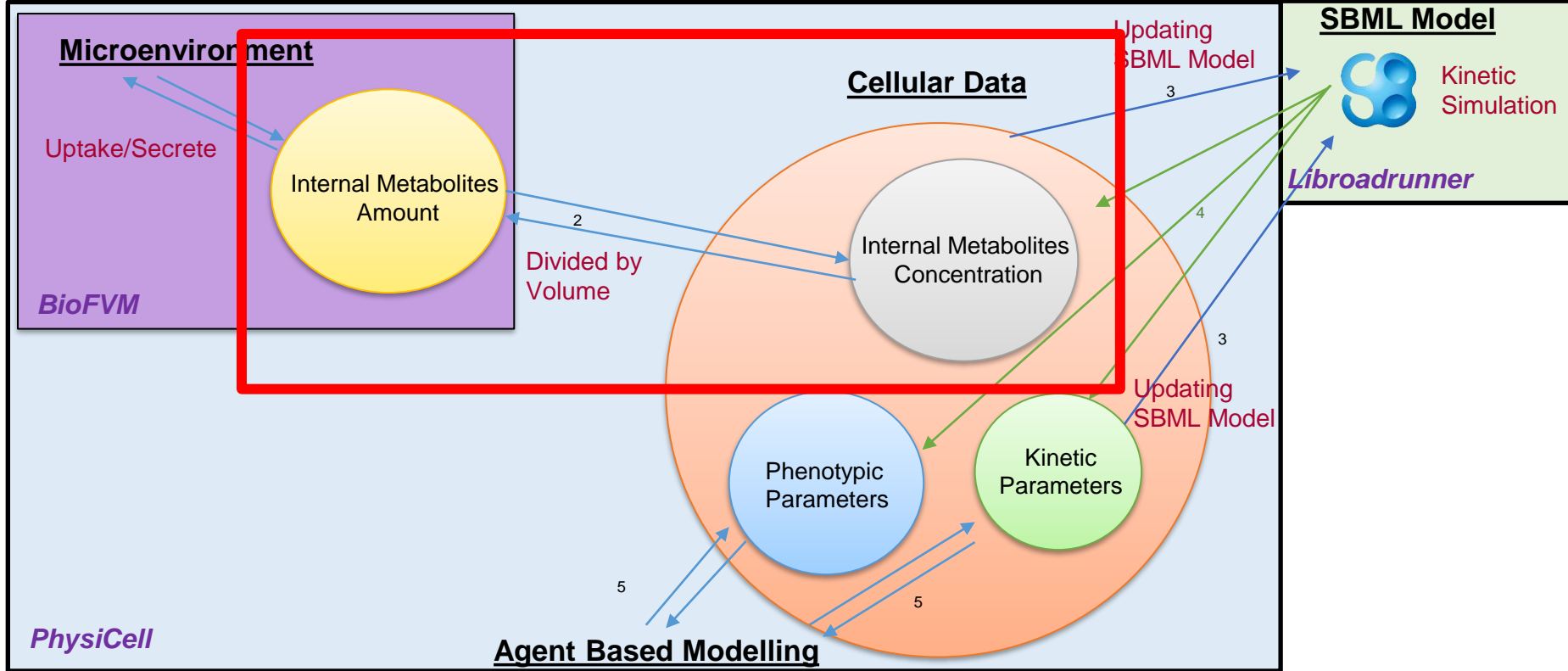
pCell->phenotype.intracellular->start();

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

Integration Design



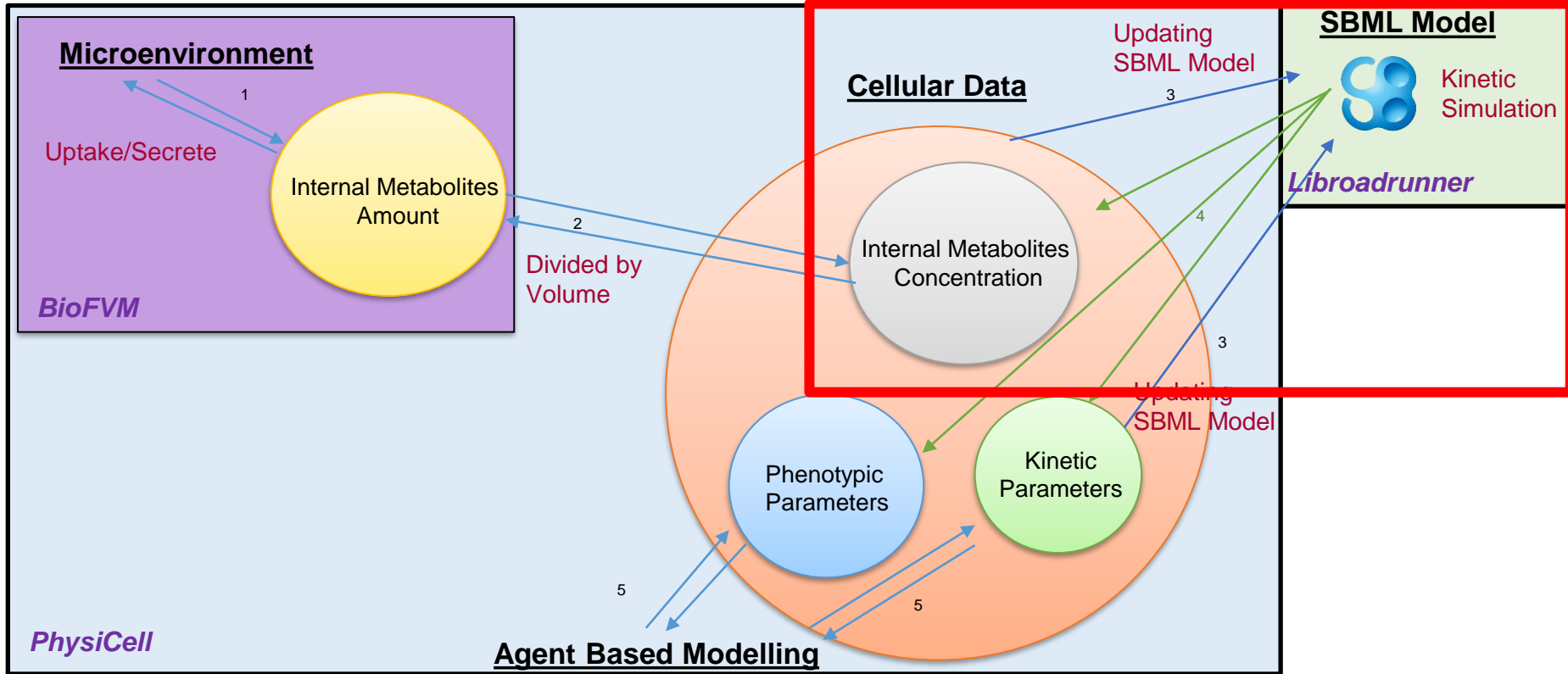
Integration Design



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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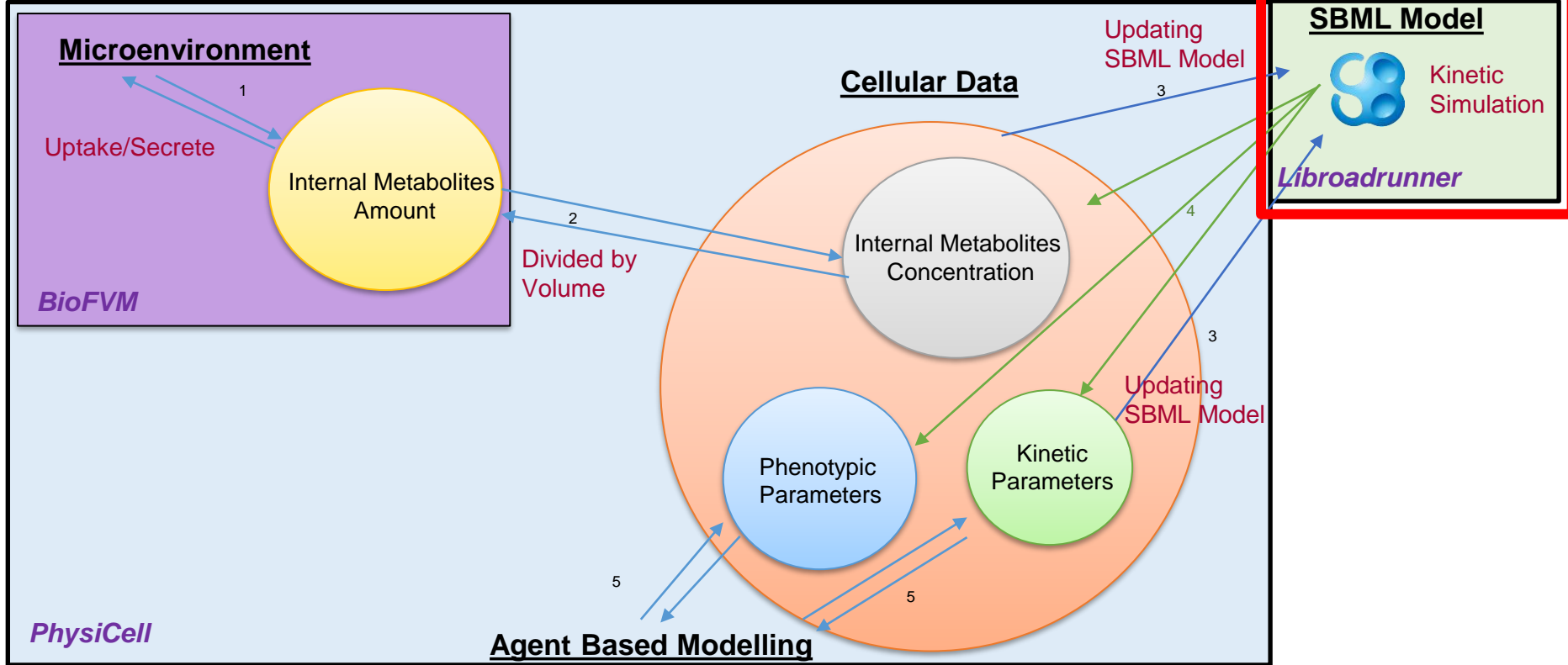
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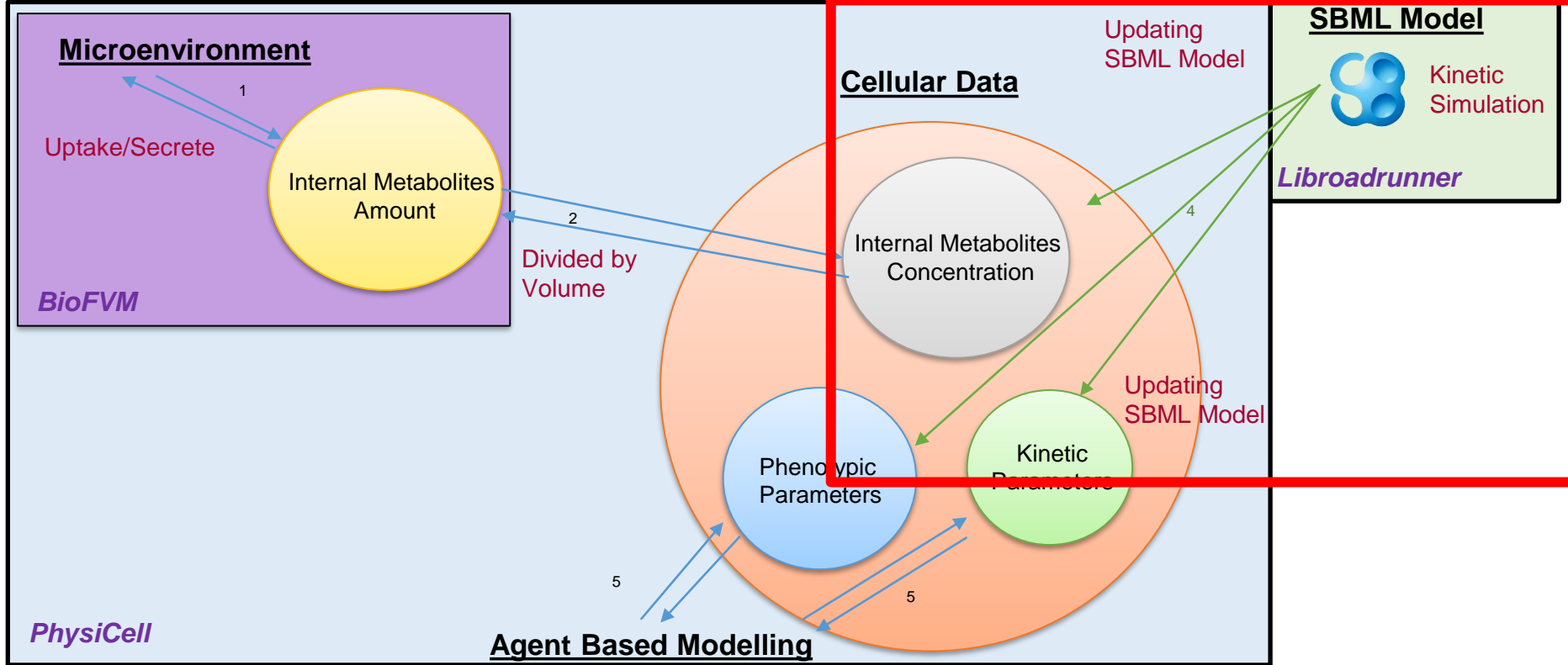
Integration Design



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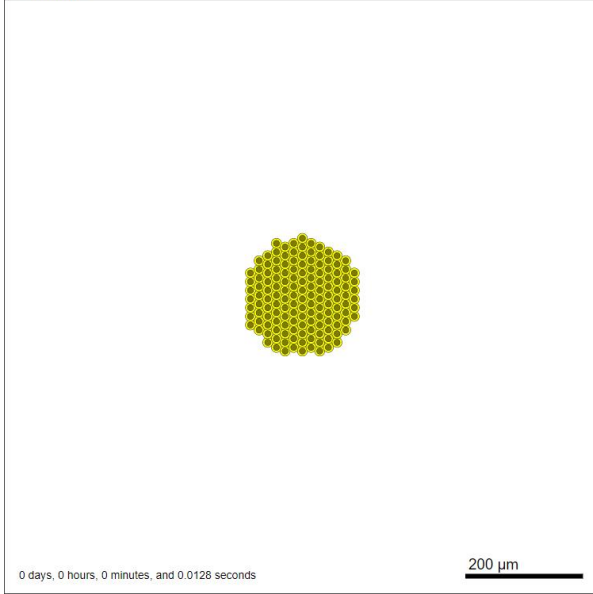
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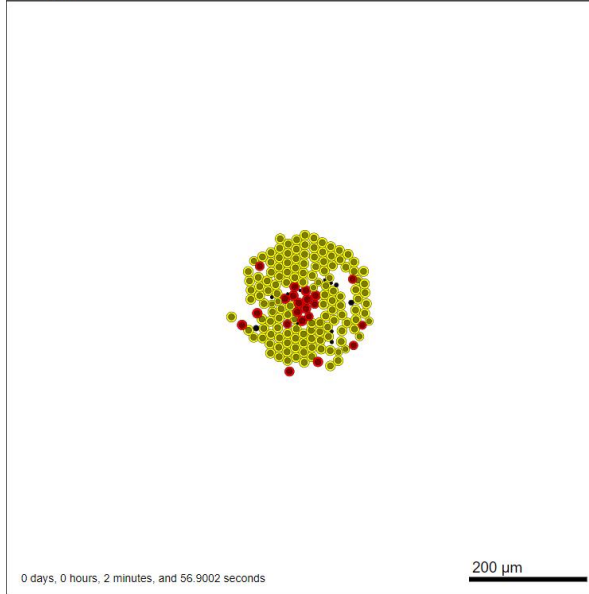
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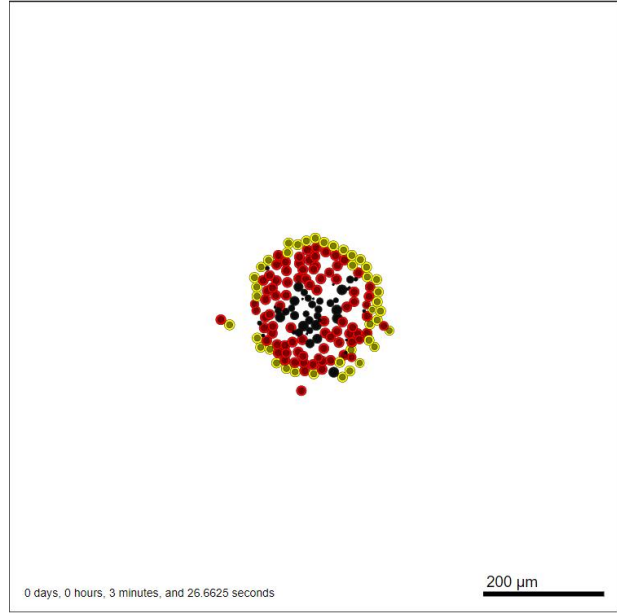
Current time: 0 days, 0 hours, and 0.00 minutes, $z = 0.00 \mu\text{m}$
144 agents



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?



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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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PhysiCell Development:

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

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