Slides, videos, links and more:
https://github.com/physicell-training/ws2023

Advanced Session 7: Intracellular with libRoadrunner (interactive demo)

Furkan Kurtoglu
@PhysiCell

PhysiCell Project

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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/lMtG44cJejM?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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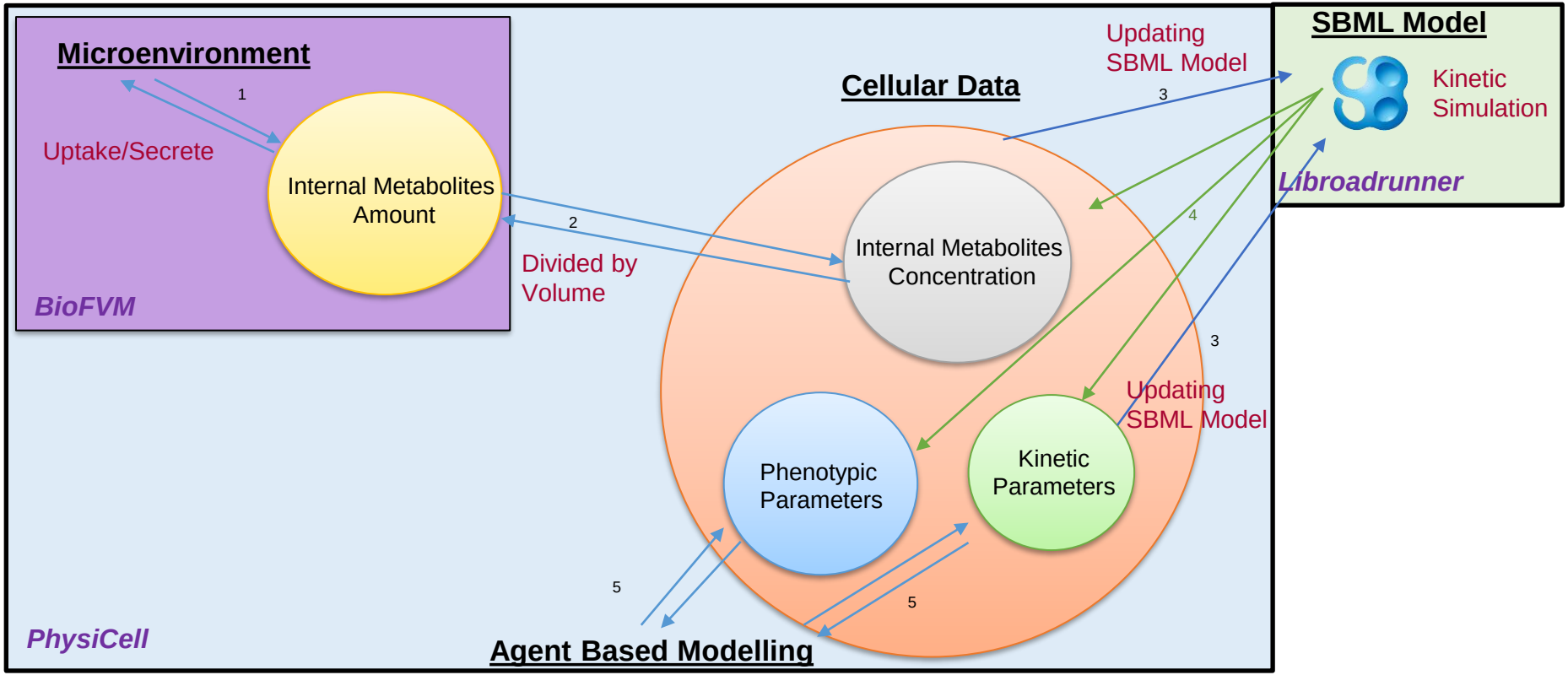
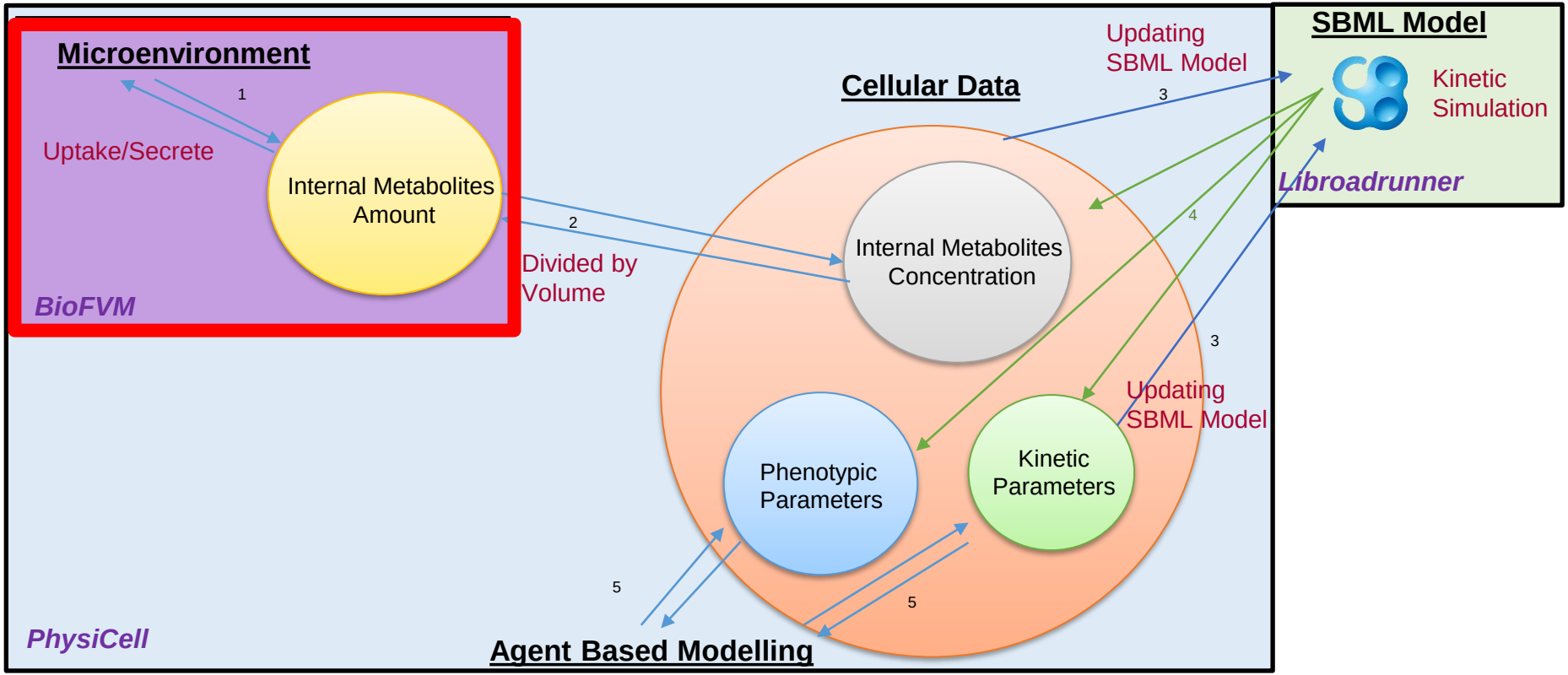
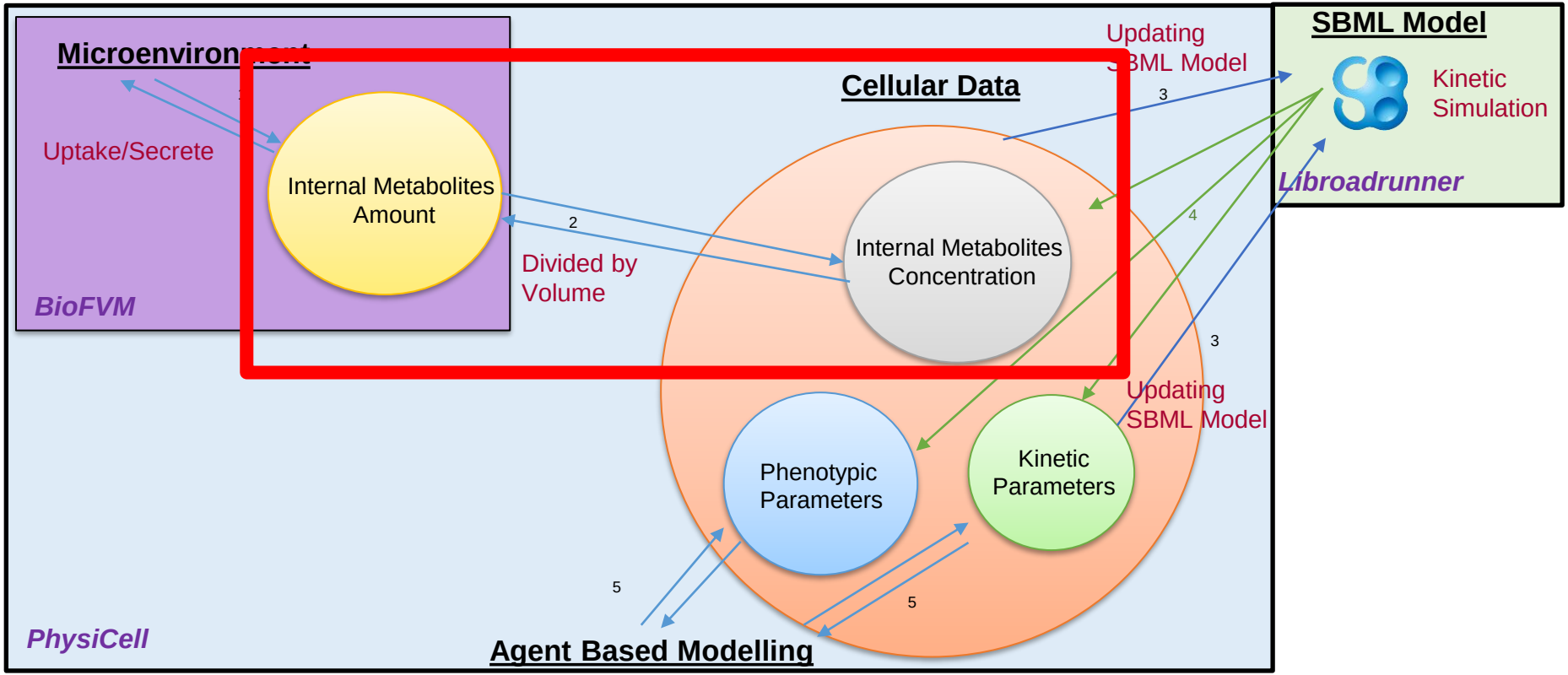
Integration Design



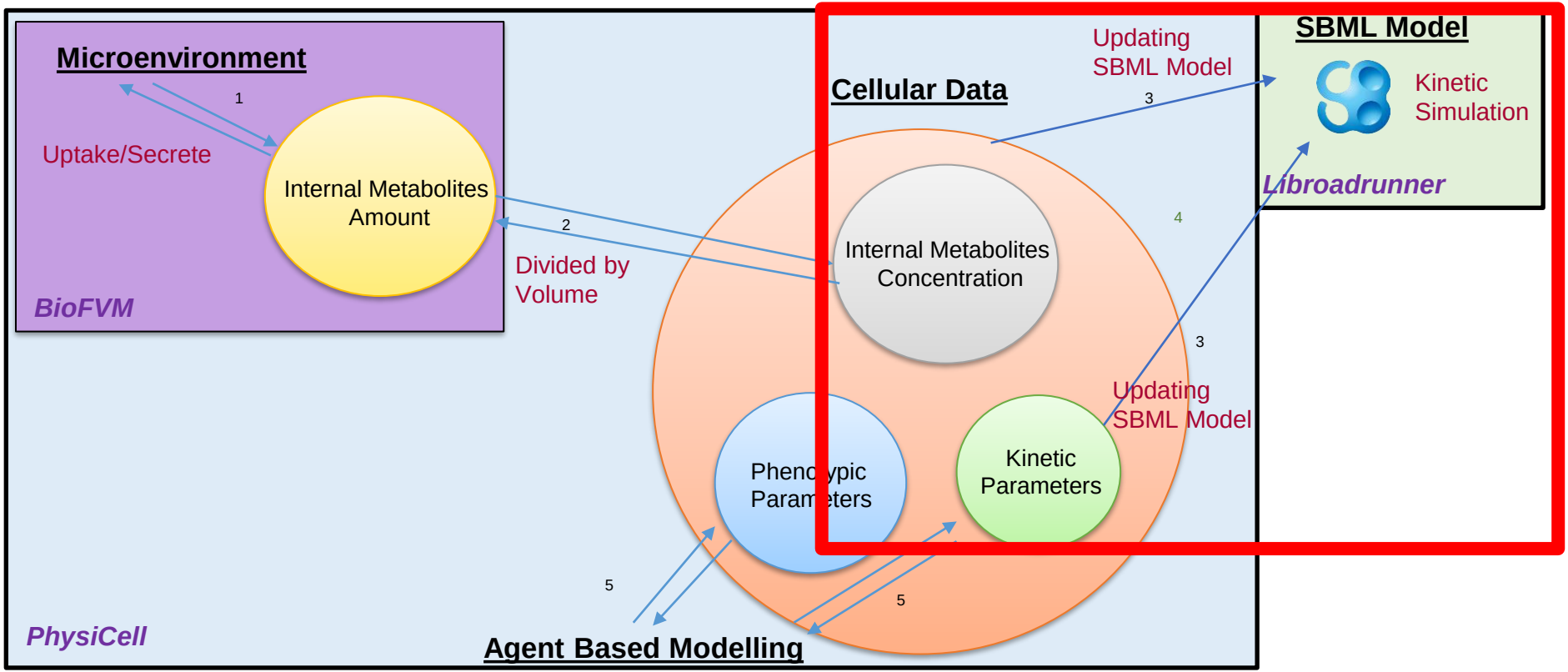
Integration Design



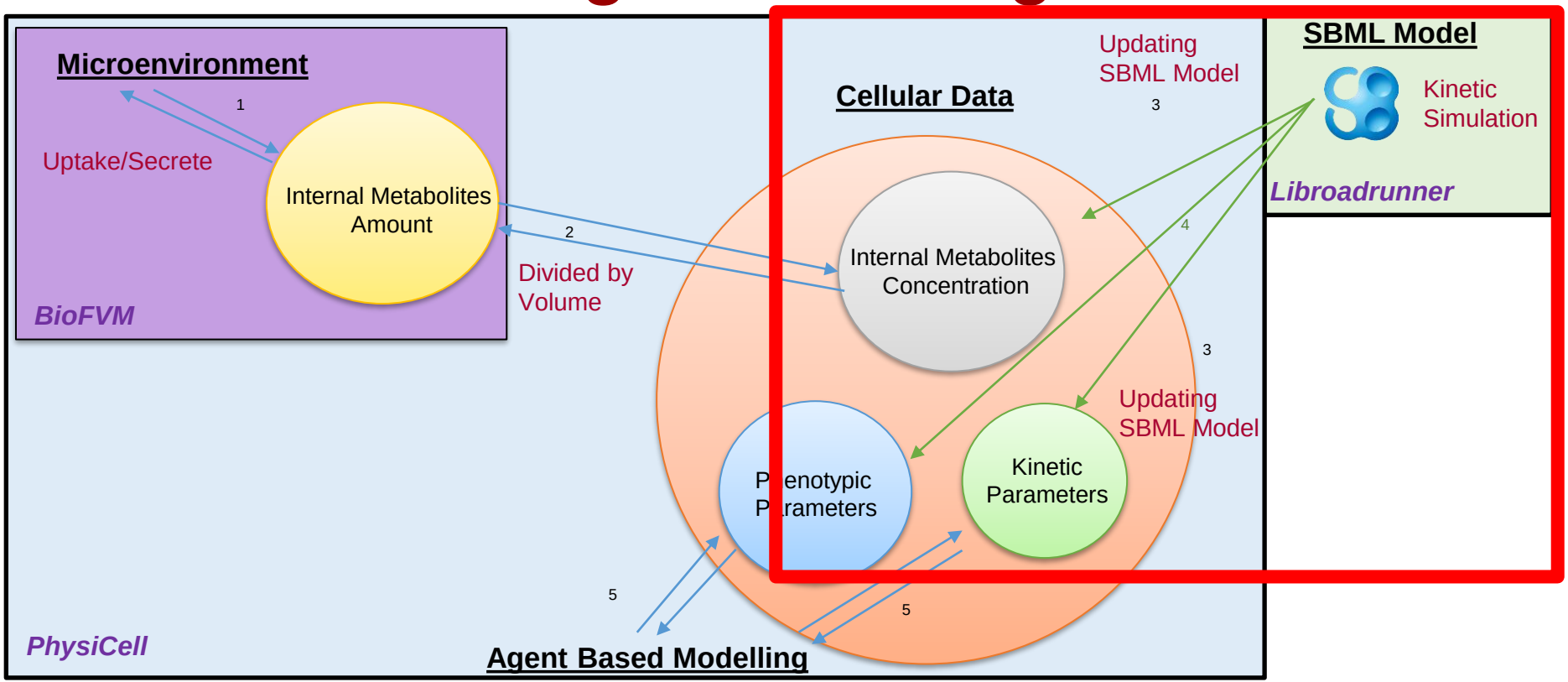
Integration Design



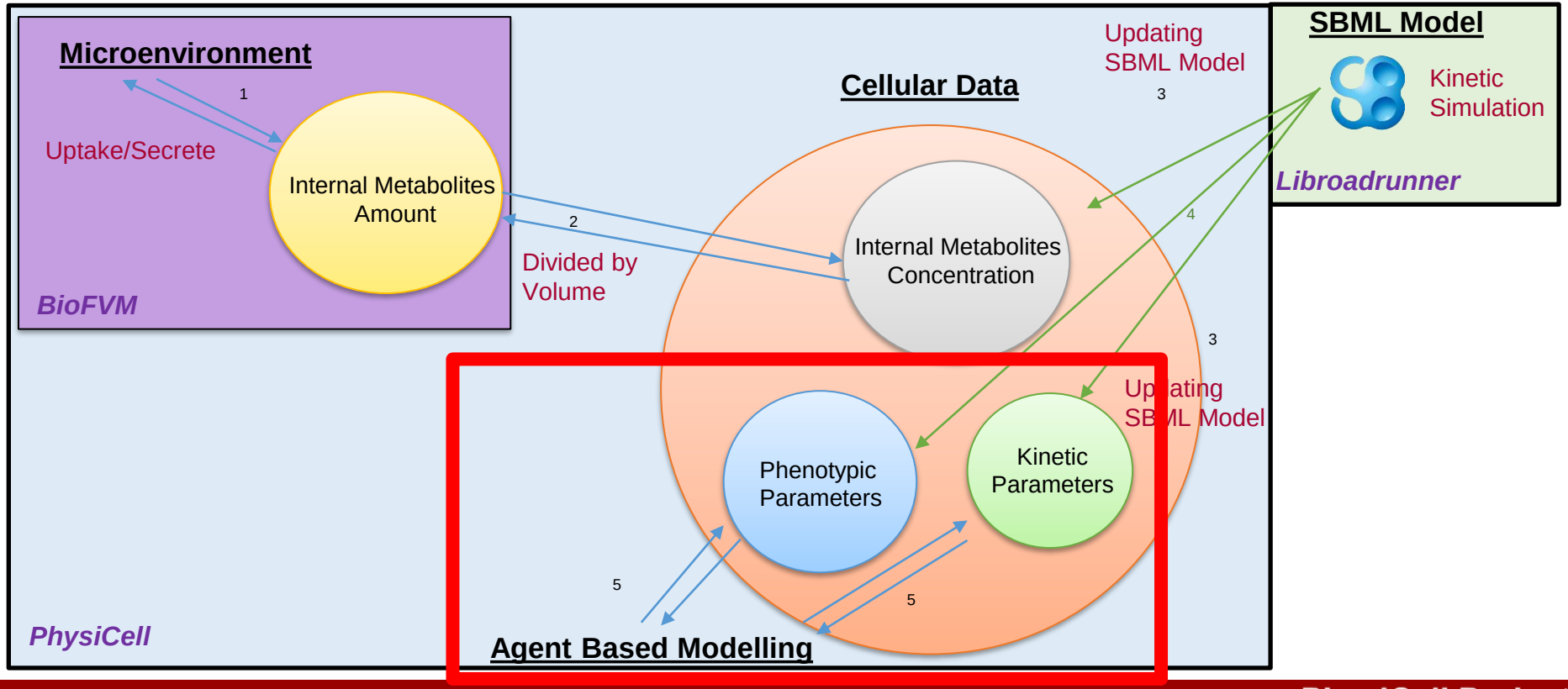
Integration Design



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

SBML Model

- Three Substrates
  - Oxygen, Glucose, Lactate
  - Energy is created with two reactions
    - Glucose + Oxygen -> 38 * Energy (Aerobic)
    - Glucose -> 4 * Energy + Lactate (Anaerobic)
  - Energy consumes
    - Energy -> (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

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

Agenda:

- Previous Session
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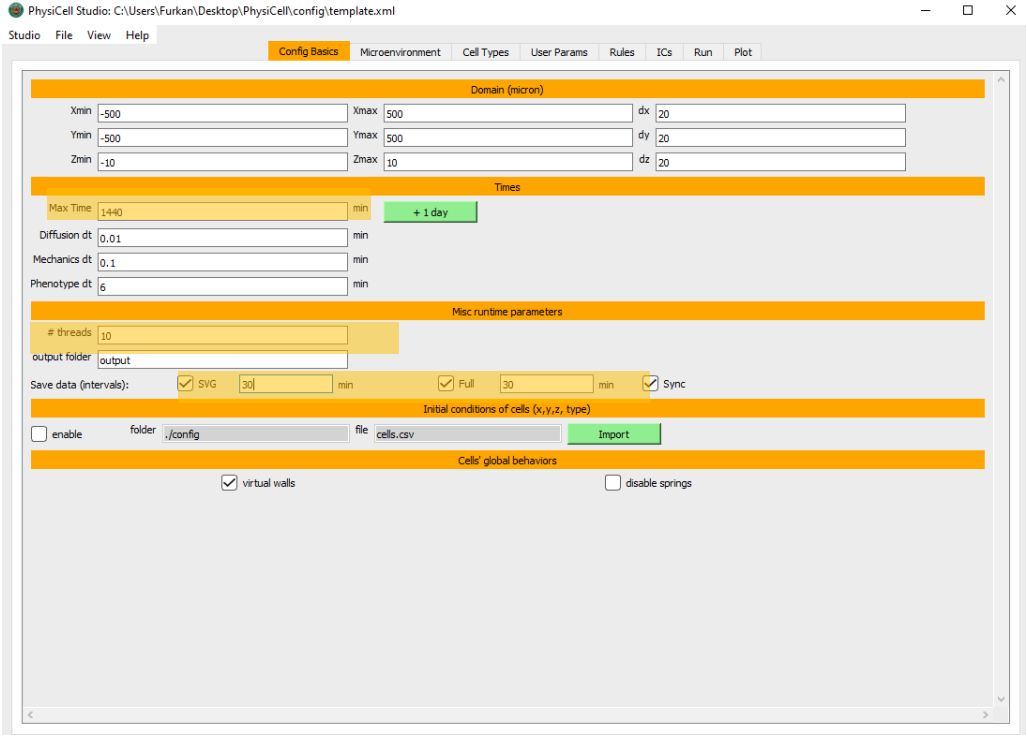
- Simulation & Analysis

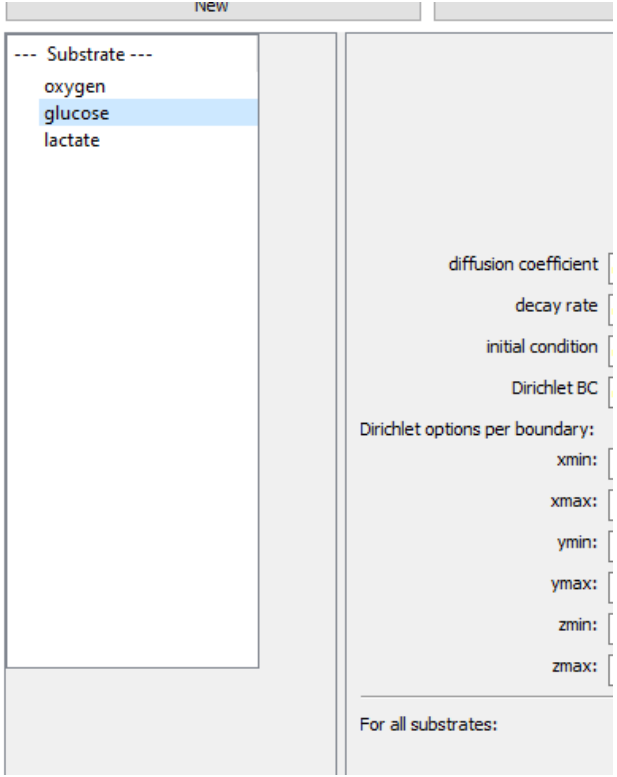
Config Basics

- 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, Full = 30 min



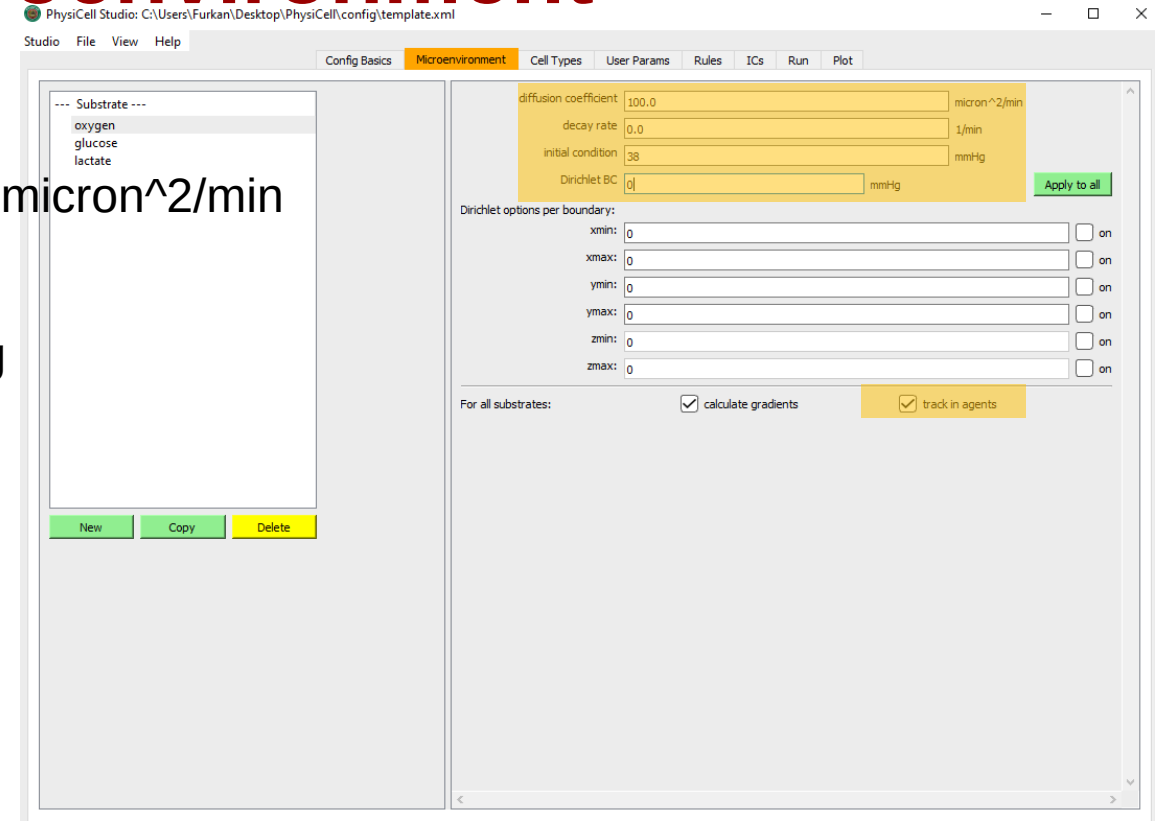
Microenvironment

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



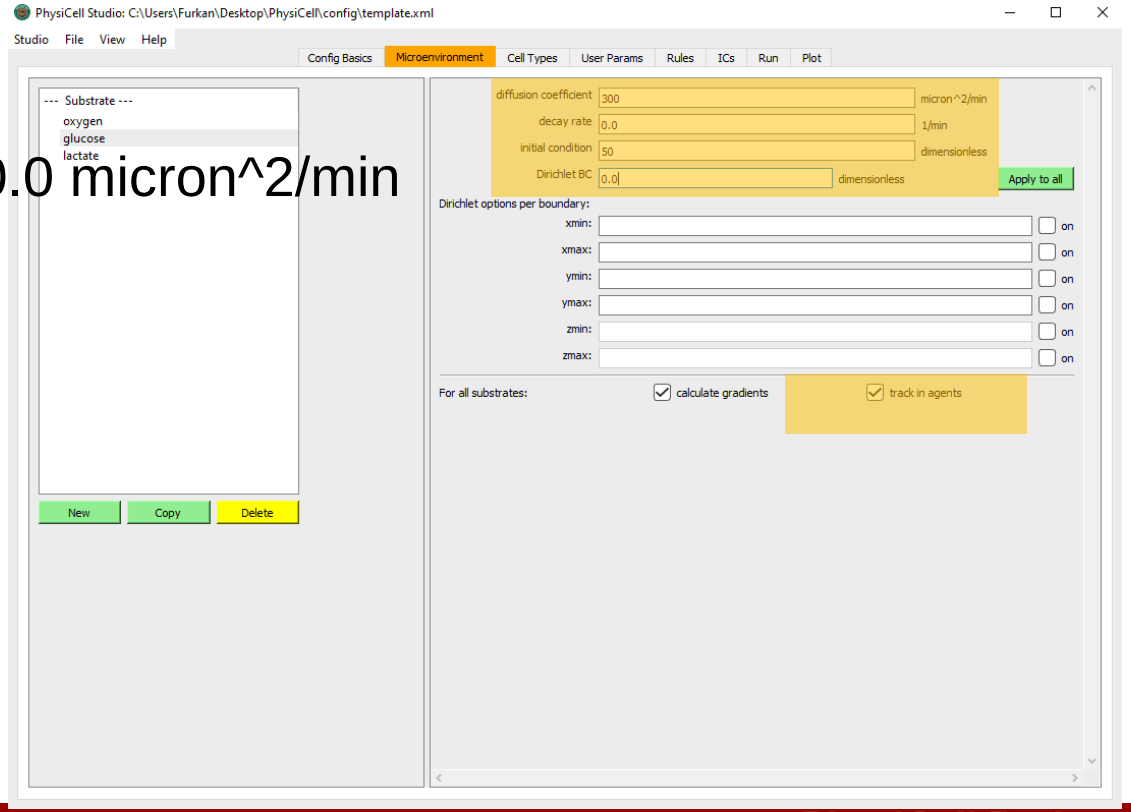
Microenvironment

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



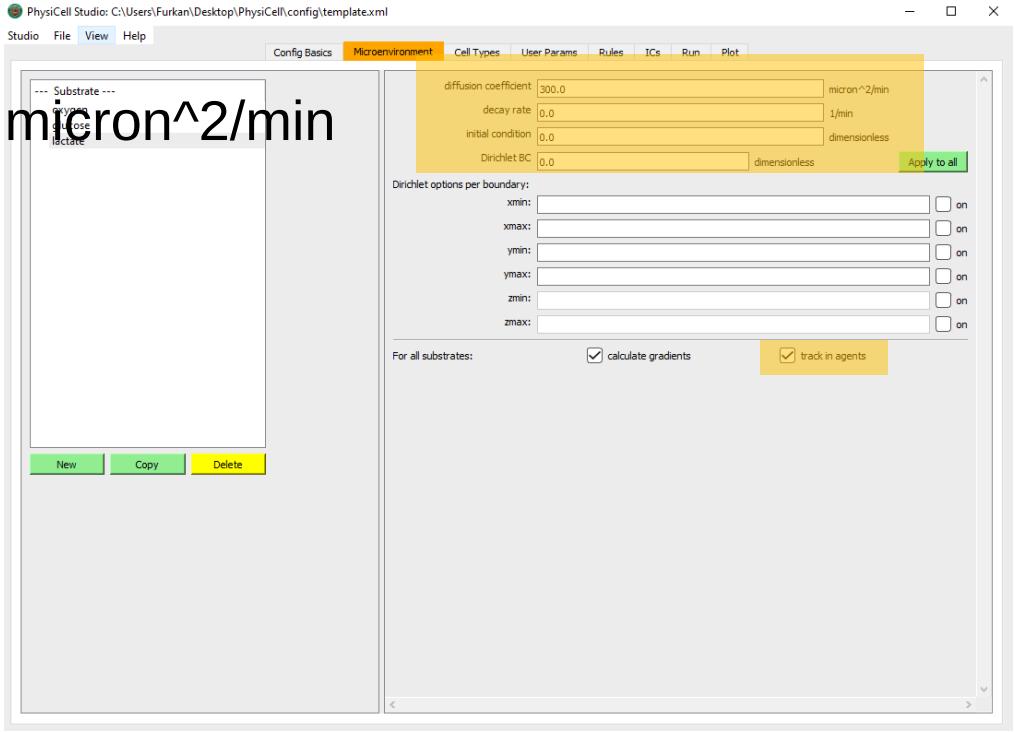
Microenvironment

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



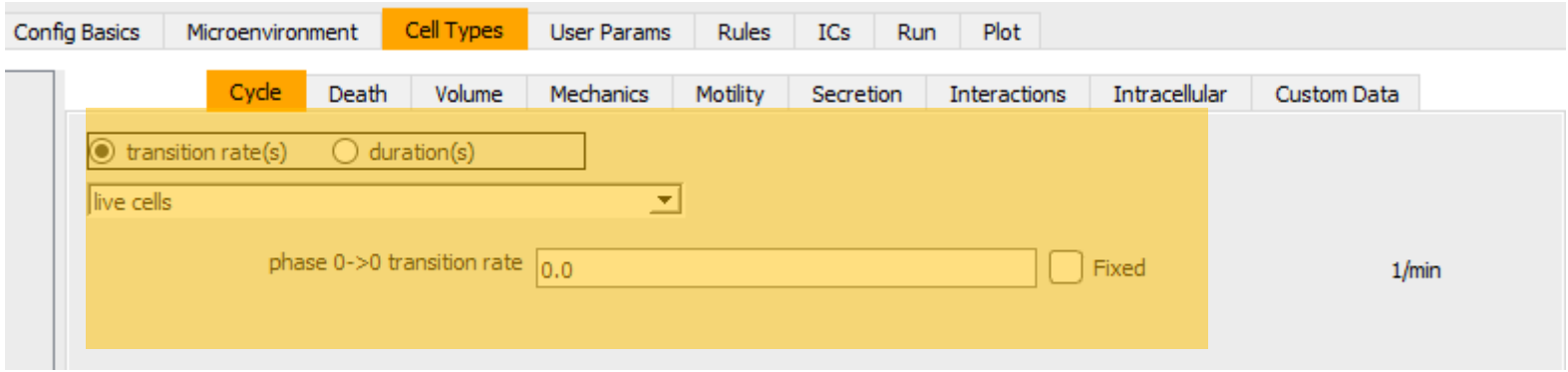
Microenvironment

- Lactate
- Diffusion Coefficient = 300.0 micron^2/min
- Decay Rate = 0.0 1/min
- Initial condition = 0.0 mmHg
- Dirichlet = OFF
- Track in agents = ON



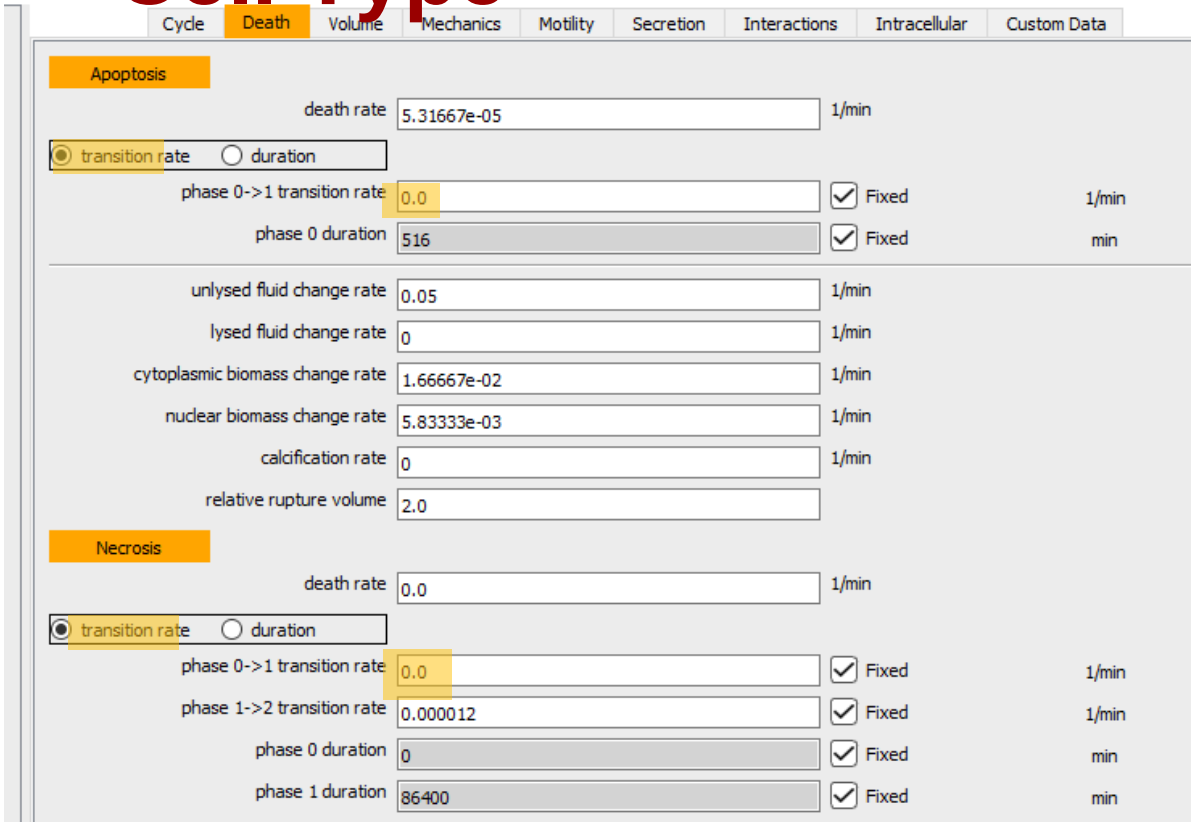
Cell Type

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



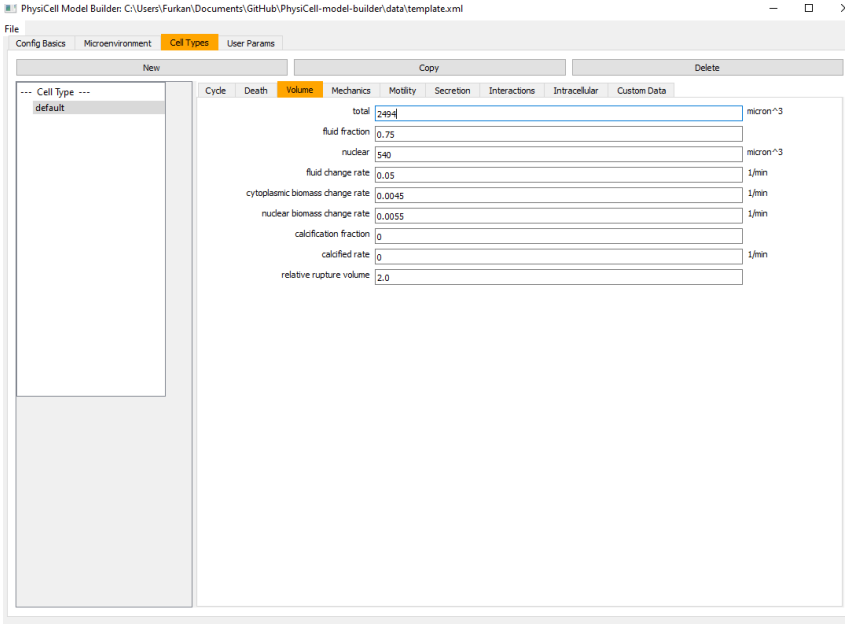
Cell Type

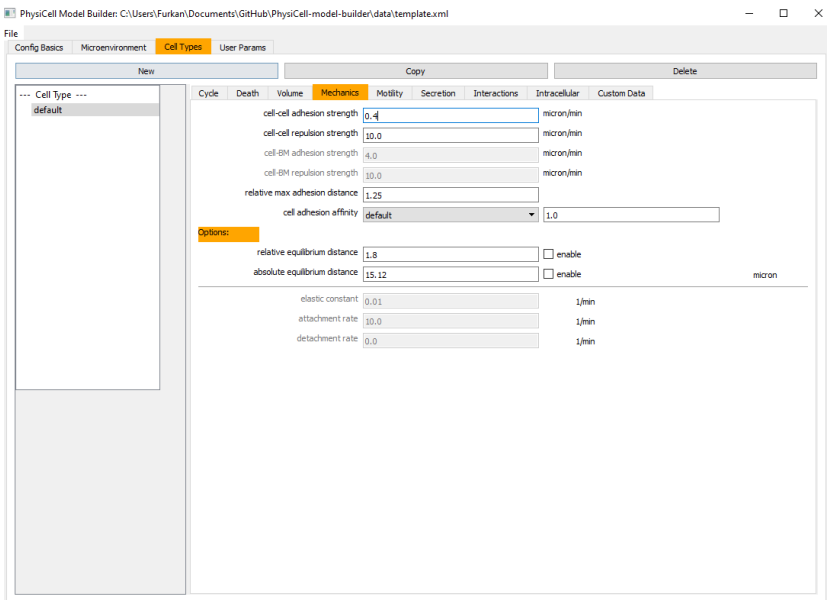
- No Death



Cell Type

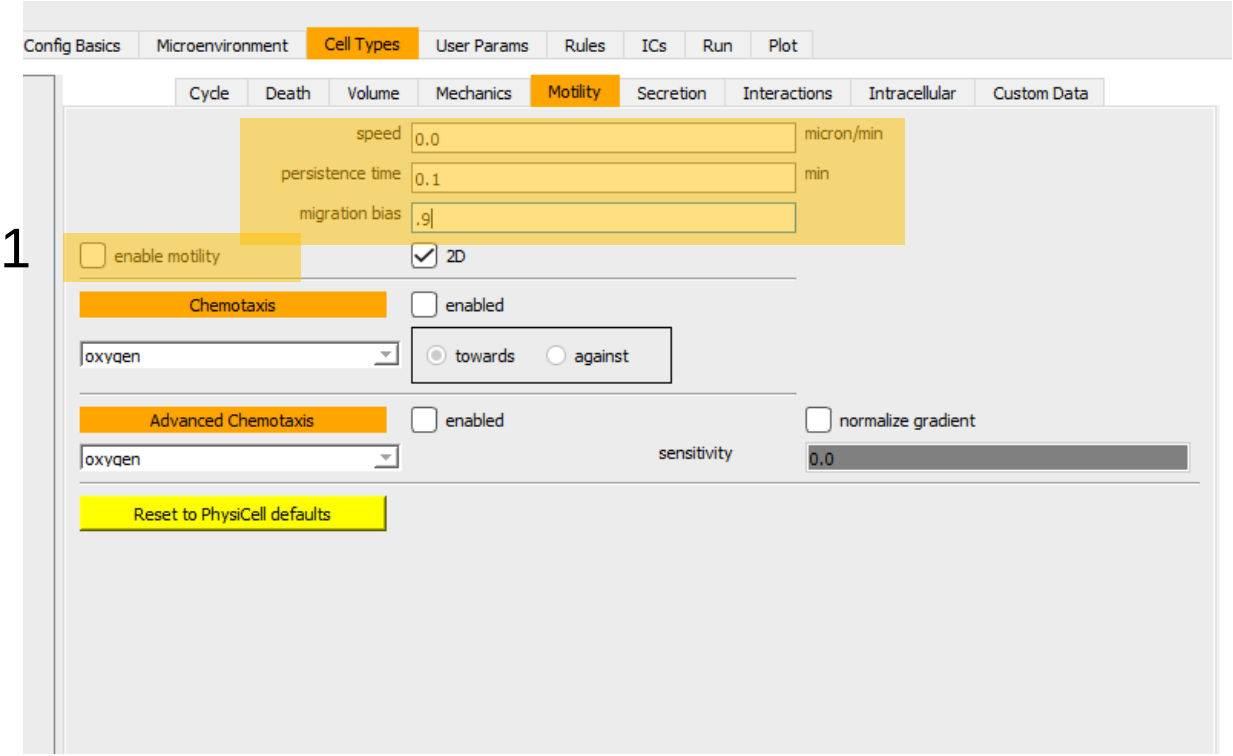
- No change in the Volume and Mechanics Tab





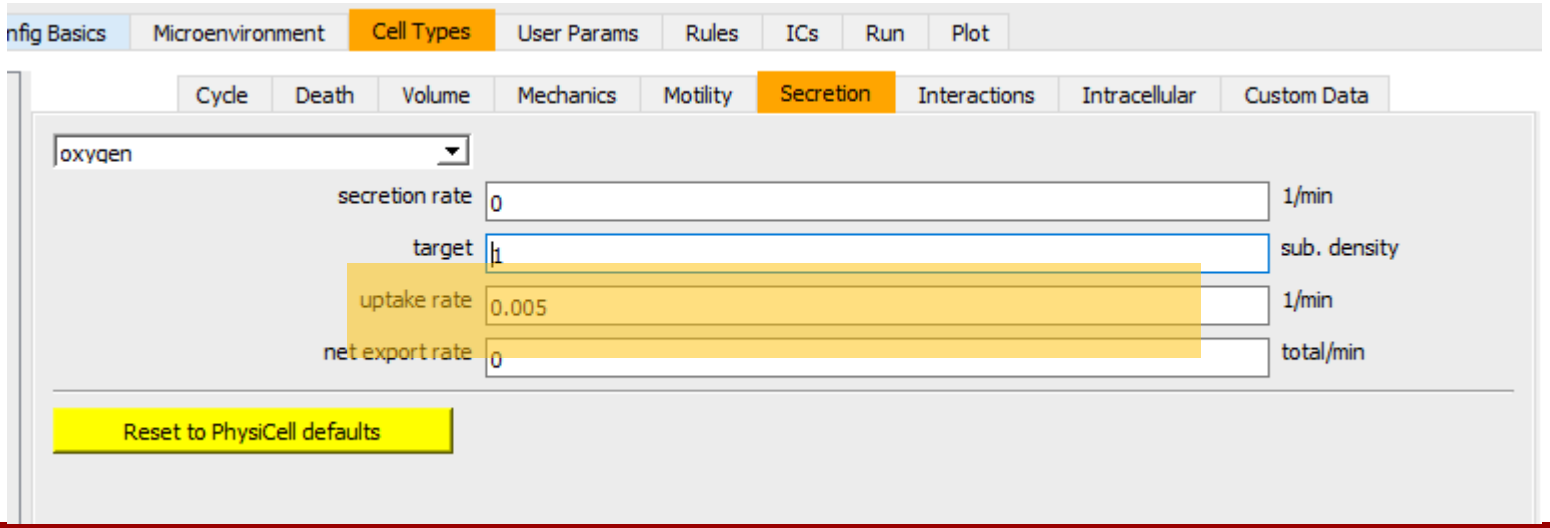
Cell Type

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



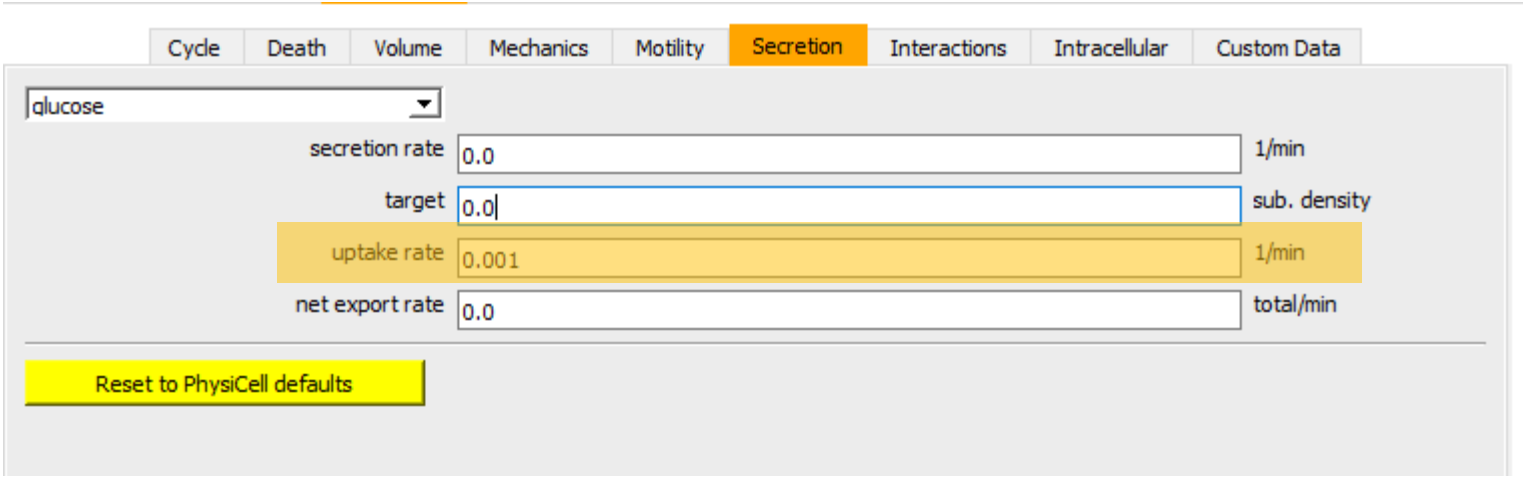
Cell Type : Secretion

- Oxygen Tab
- Uptake rate = 0.005



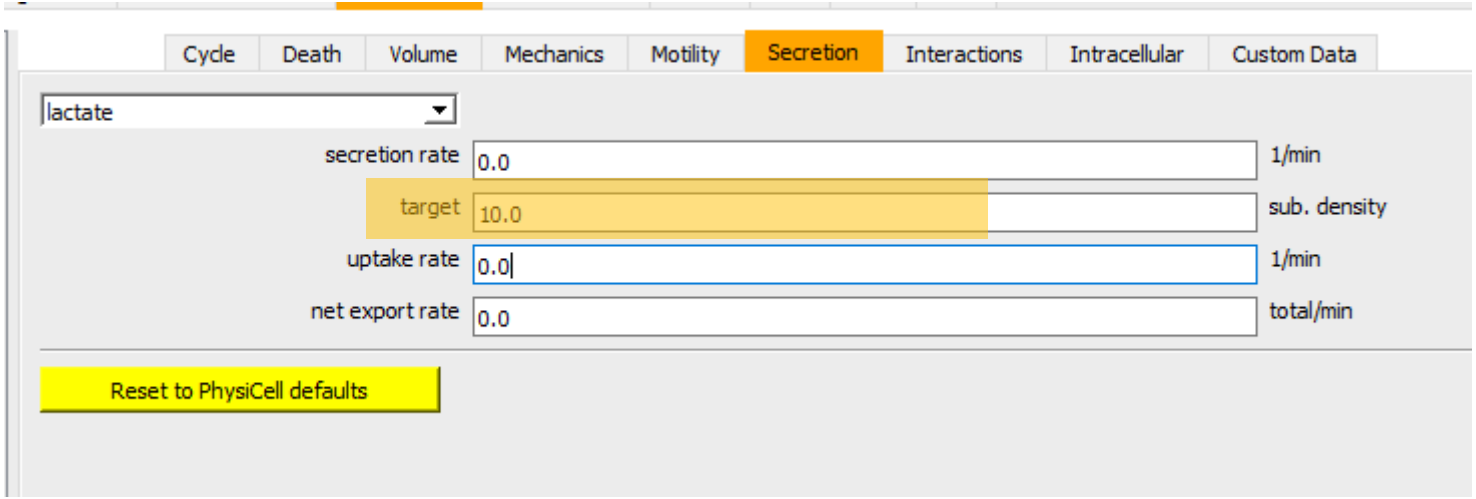
Cell Type : Secretion

- Glucose Tab
- Uptake rate = 0.001



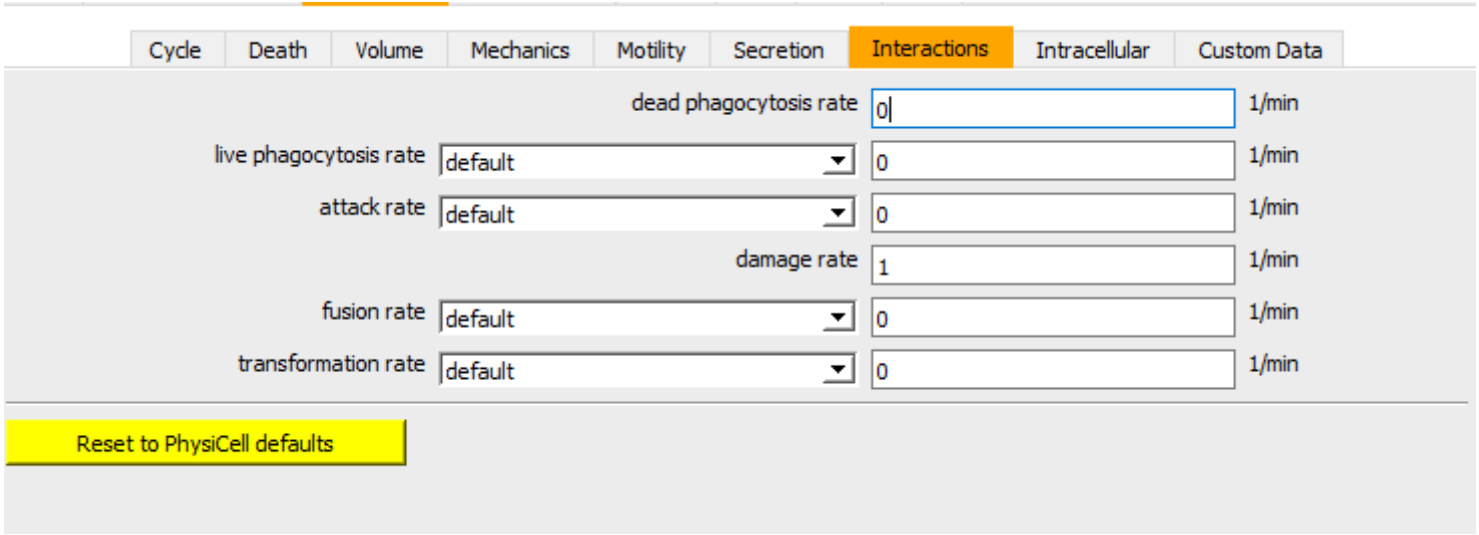
Cell Type : Secretion

- Lactate Tab
- Secretion Target = 10.0



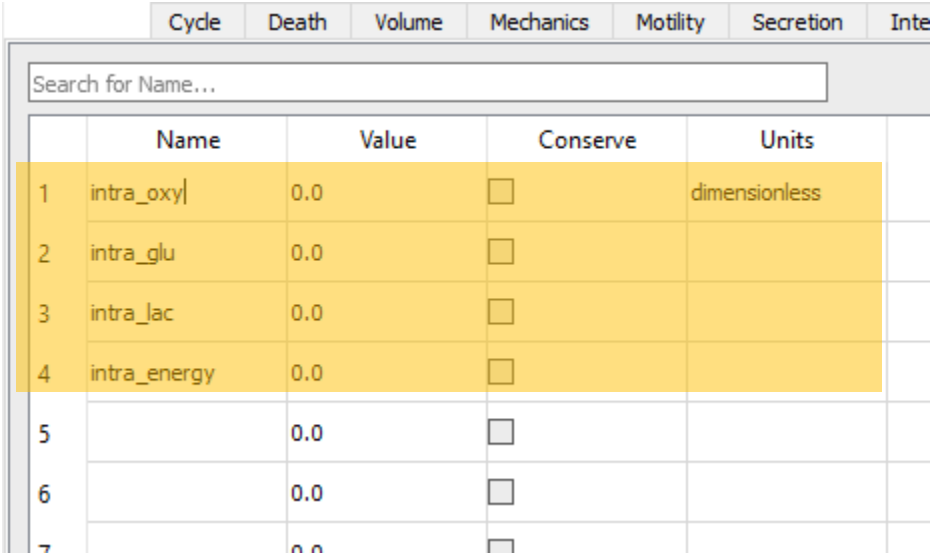
Cell Type

- No Interactions



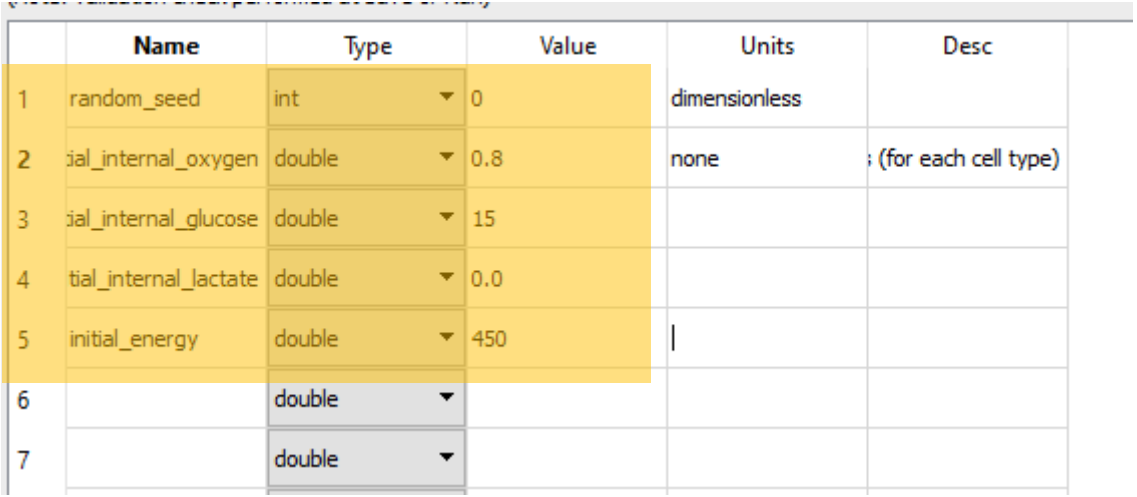
Cell Custom Data

- We need to create intracellular data to save the data
- intra_oxy = 0.0
- intra_glu = 0.0
- intra_lac = 0.0
- intra_energy = 0.0



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	ial_internal_oxygen	double	0.8	none	; (for each cell type)
3	ial_internal_glucose	double	15		
4	tial_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

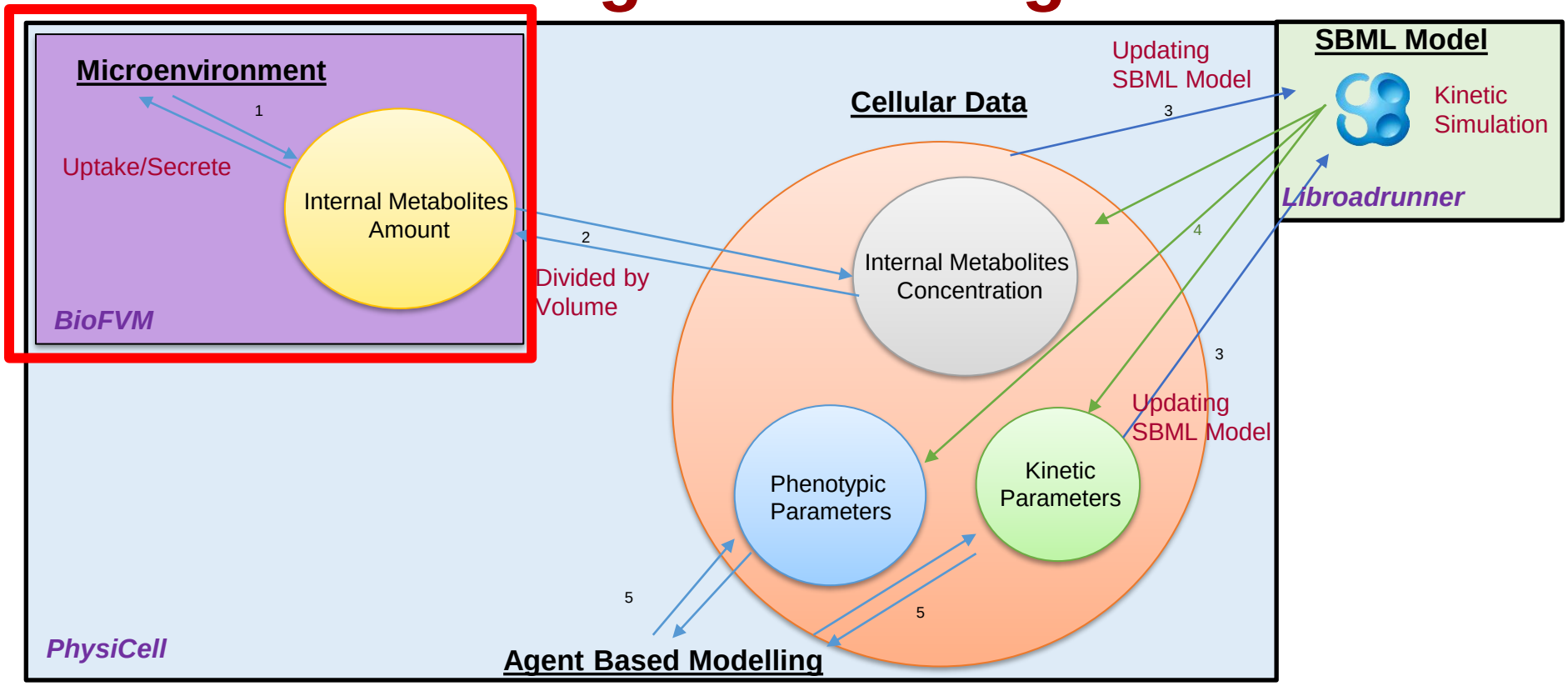
- We will remove intracellular-related parts
- And build one-by-one
- At custom.cpp
  - setup_tissue():
    - Remove lines between #174-198
  - update_intracellular():
    - Remove anything in if loop #216-245
      - Beware line numbers might shift after first removal

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

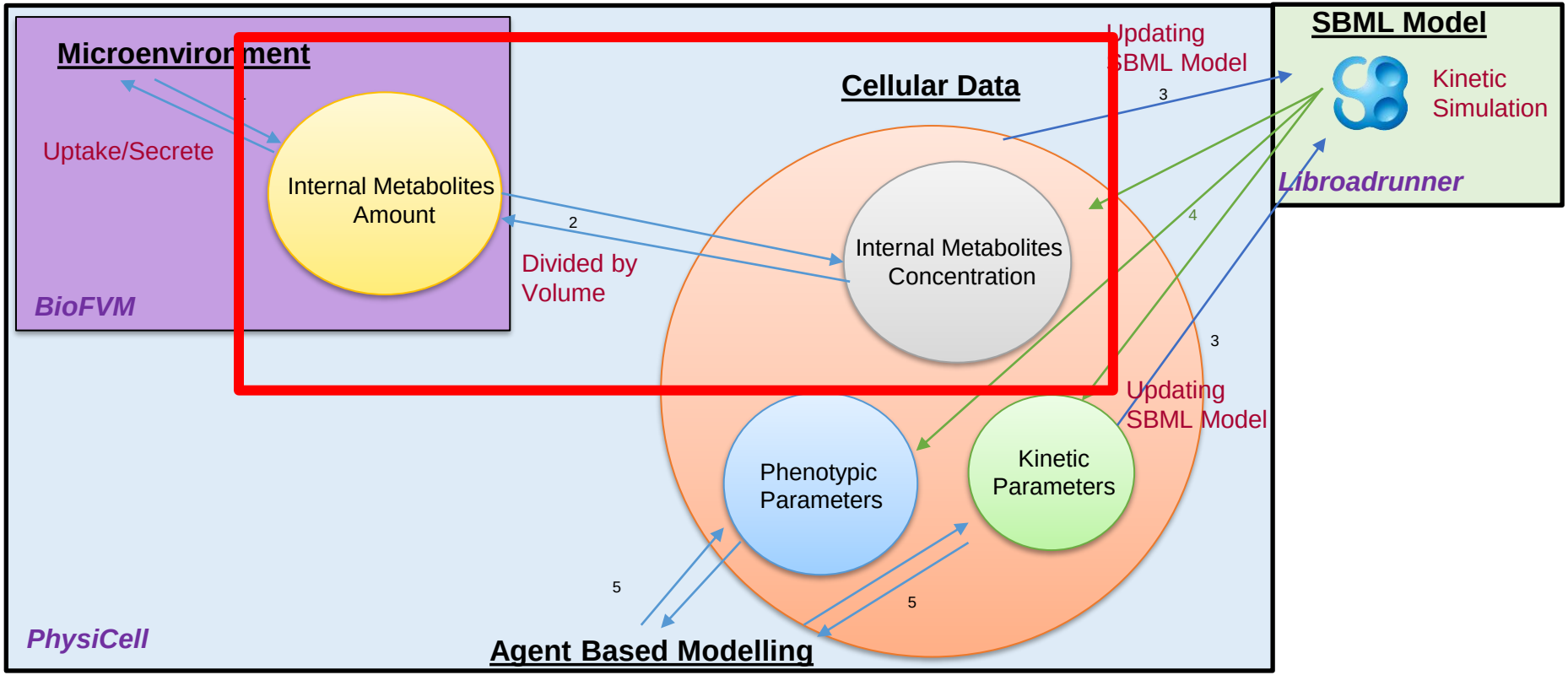
setup_tissue(): after cell seeding

```
// 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



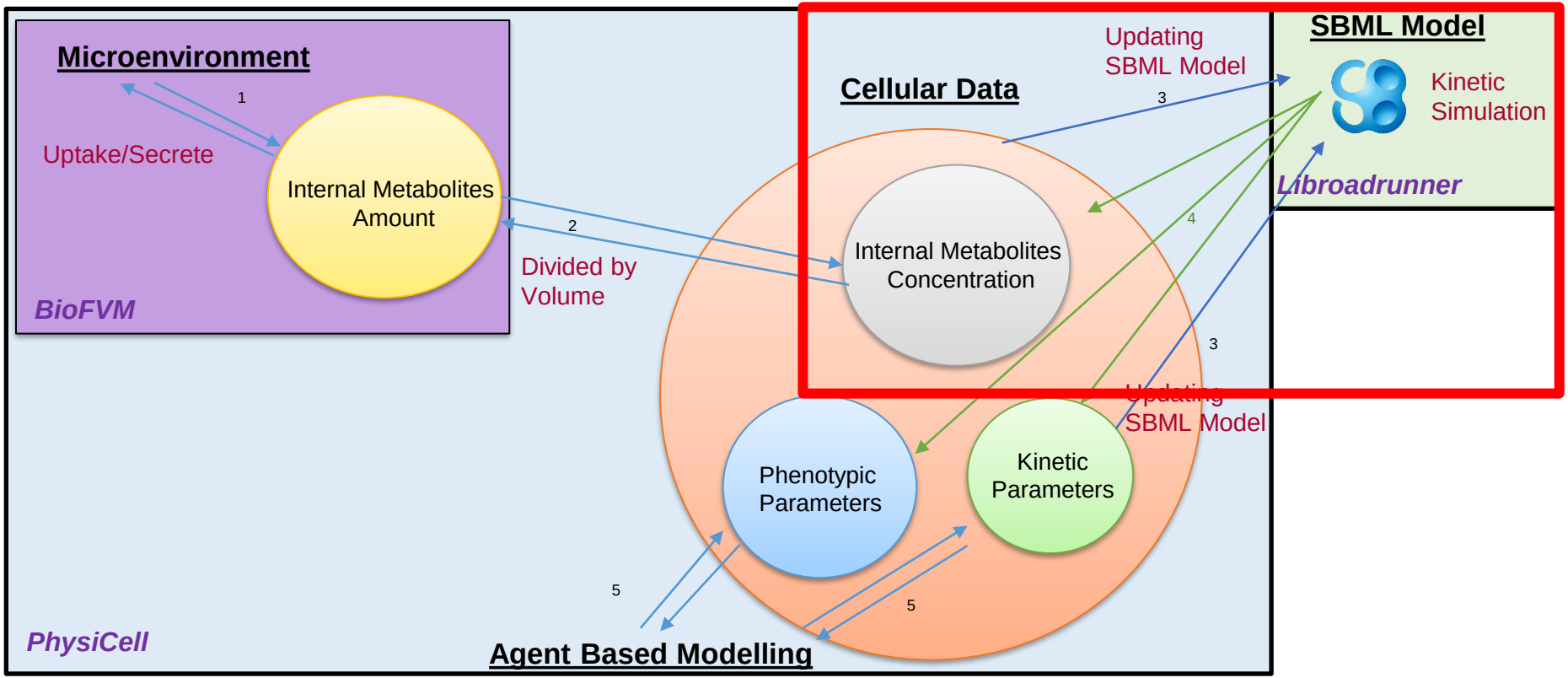
Integration Design



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");
```

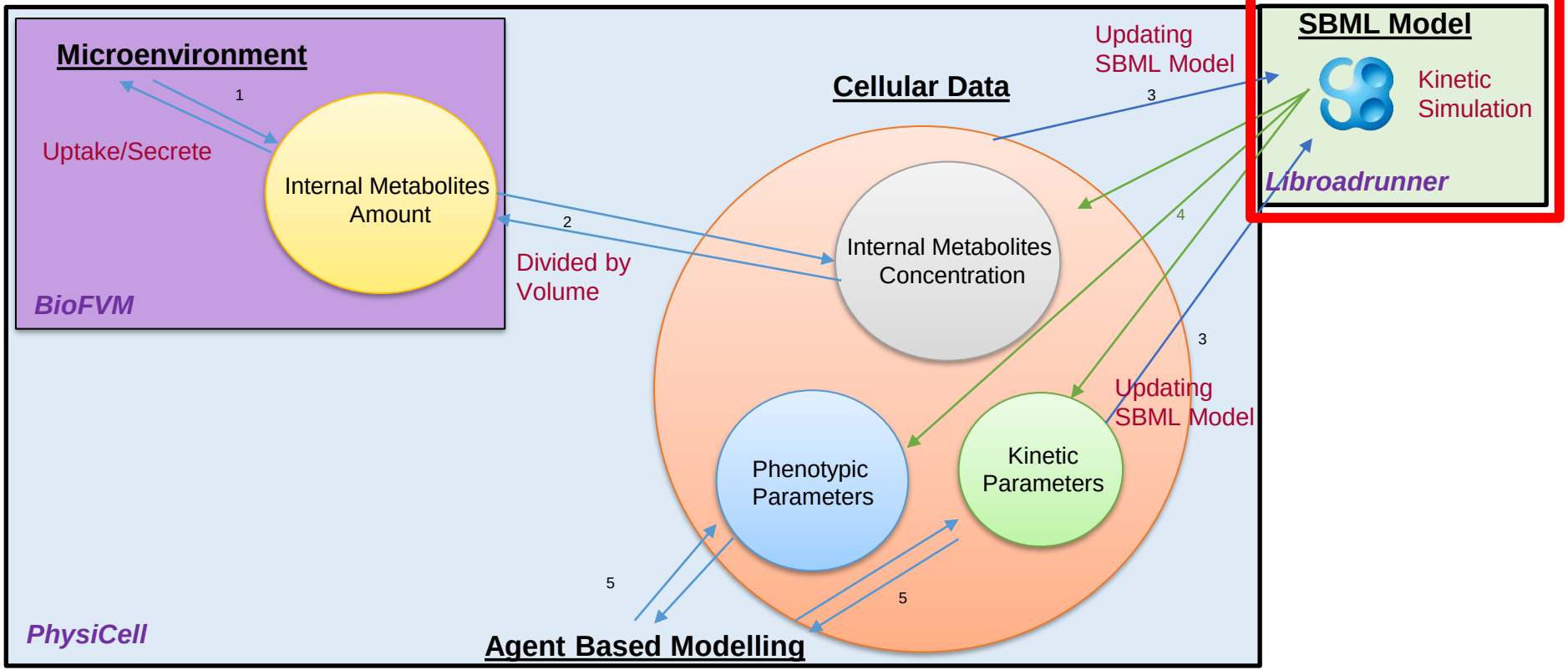
Integration Design



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);
```

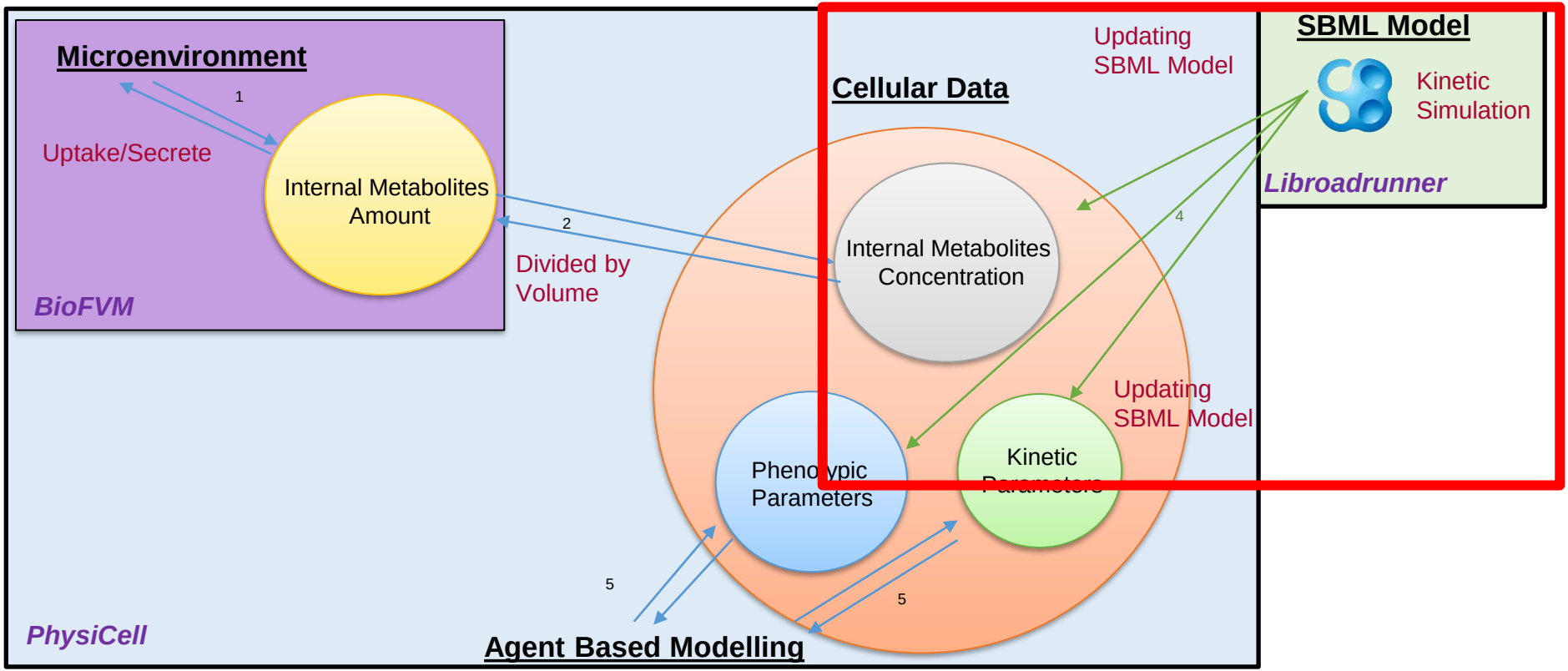
Integration Design



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

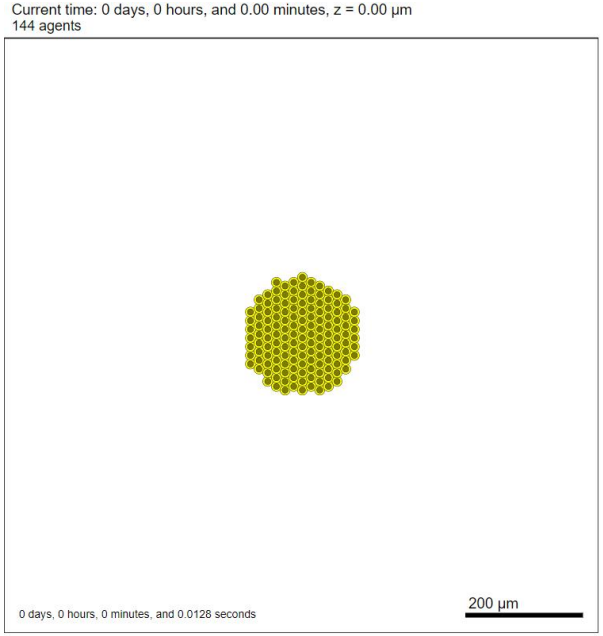
```
// Internalized Chemical Update After SBML Simulation

(*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.intrac
>get_parameter_value("Oxygen") );

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

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

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

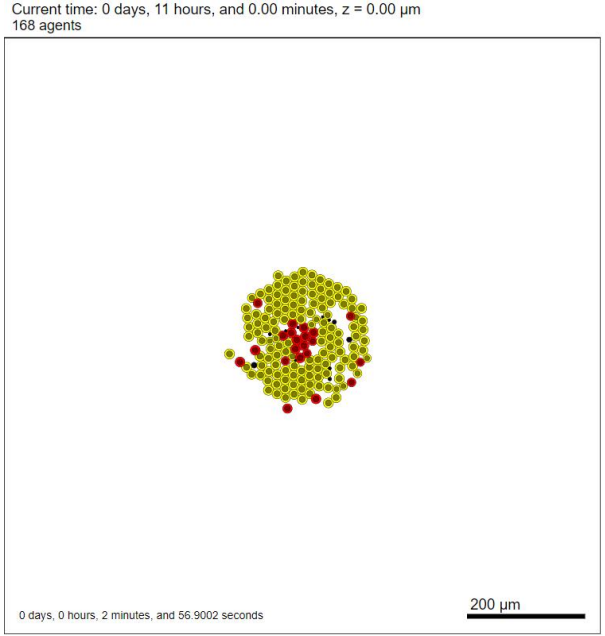
Let’s Simulate

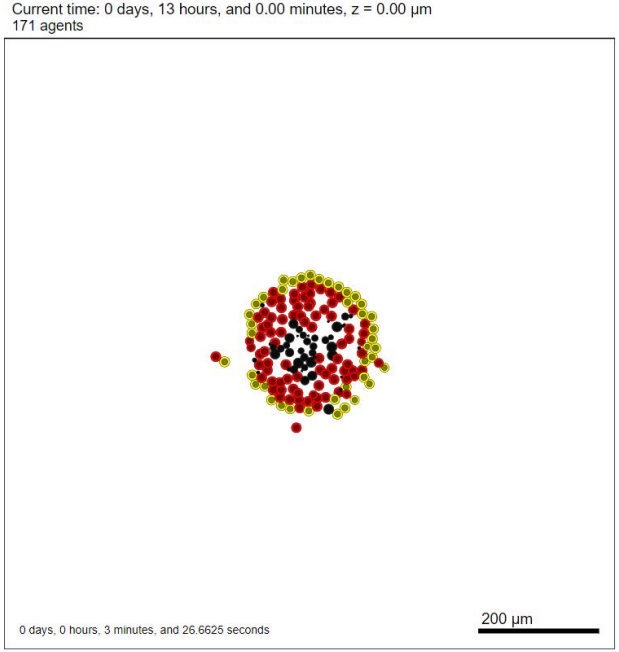
- I will use beta/plot_cells.py and beta/plot_data for analysis

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

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


Current time: 0 days, 0 hours, and 0.00 minutes, z = 0.00 μm
144 agents
0 days, 0 hours, 0 minutes, and 0.0128 seconds
200 μm


Current time: 0 days, 11 hours, and 0.00 minutes, z = 0.00 μm
168 agents
0 days, 0 hours, 2 minutes, and 56.9002 seconds
200 μm


Current time: 0 days, 13 hours, and 0.00 minutes, z = 0.00 μm
171 agents
0 days, 0 hours, 3 minutes, and 26.6625 seconds
200 μm

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

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)