

Vivarium: a compositional framework for multiscale modeling



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Different biological questions require different models and different formalisms

Whereas traditional systems biology models focus on the structure or dynamics of specific subsystems in controlled conditions...

Compositional systems biology aims to connect these models, asking questions about the *space between models*.

Metabolism: Flux balance analysis

$$\begin{aligned} \text{maximize} \quad & Z = c^T v \quad (\text{e.g., biomass production}) \\ \text{subject to} \quad & S \cdot v = 0 \quad (\text{steady-state mass balance}) \\ & v_{\min} \leq v \leq v_{\max} \quad (\text{flux bounds}) \end{aligned}$$

Morphogen gradient: Partial differential equations

$$\frac{\partial C(x, t)}{\partial t} = D \frac{\partial^2 C}{\partial x^2} + S(x) - \lambda C$$

Gene expression: Ordinary differential equations

$$\frac{dr}{dt} = \alpha - \gamma_r r, \quad \frac{dp}{dt} = \beta r - \gamma_p p$$

Multicellular interactions: Agent-Based Model

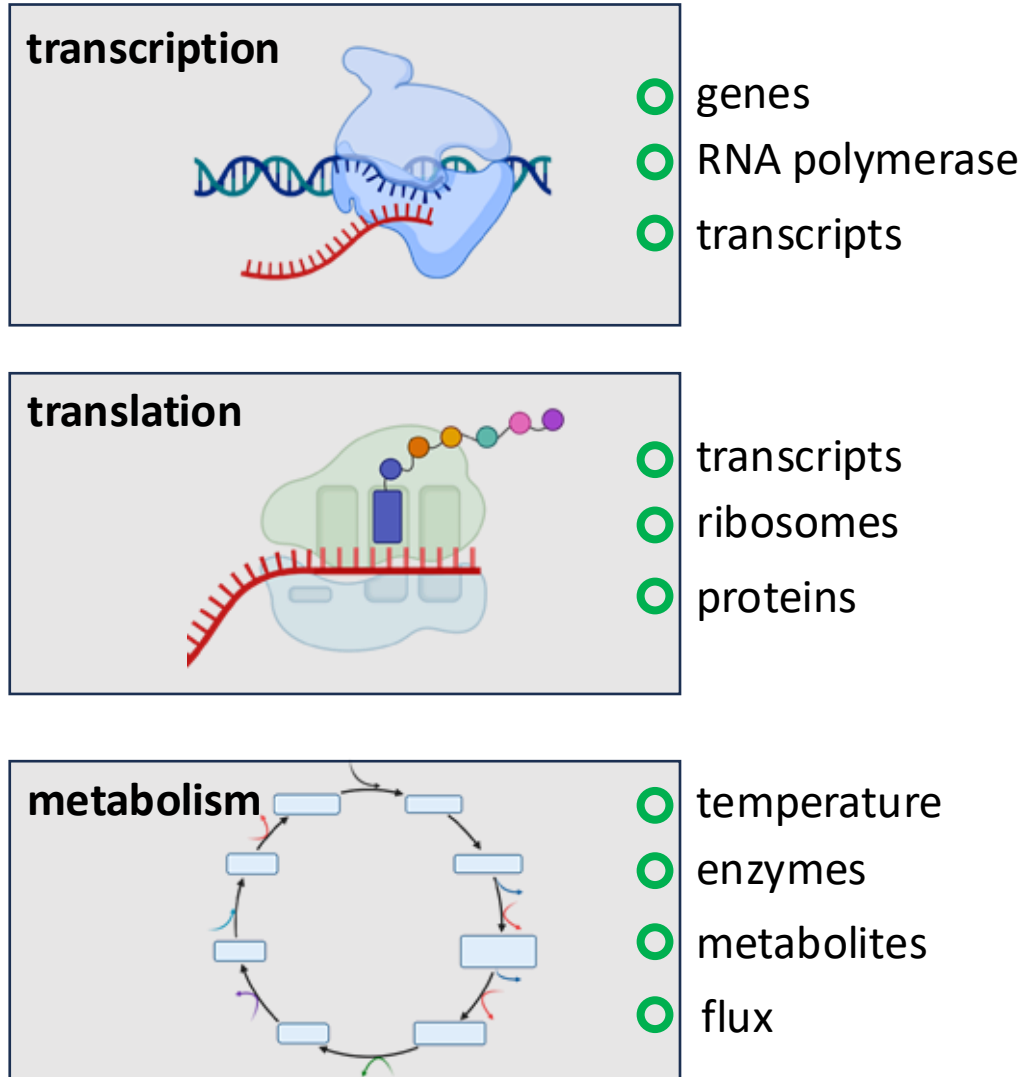
$$\begin{aligned} \vec{x}_i(t + \Delta t) &= \vec{x}_i + \mu f_{\text{int}} + \chi \nabla C + \eta \xi(t) \\ P_{\text{kill}} &= \text{Prob}(\text{kill}) \cdot \mathbf{1}_{\|\vec{x}_i - \vec{x}_j\| < d} \end{aligned}$$

Composition starts with interfaces

Whereas traditional systems biology models focus on the structure or dynamics of specific subsystems in controlled conditions...

Compositional systems biology aims to connect these models, asking questions about the *space between models*.

- **What variables should a submodel expose through its interface?**

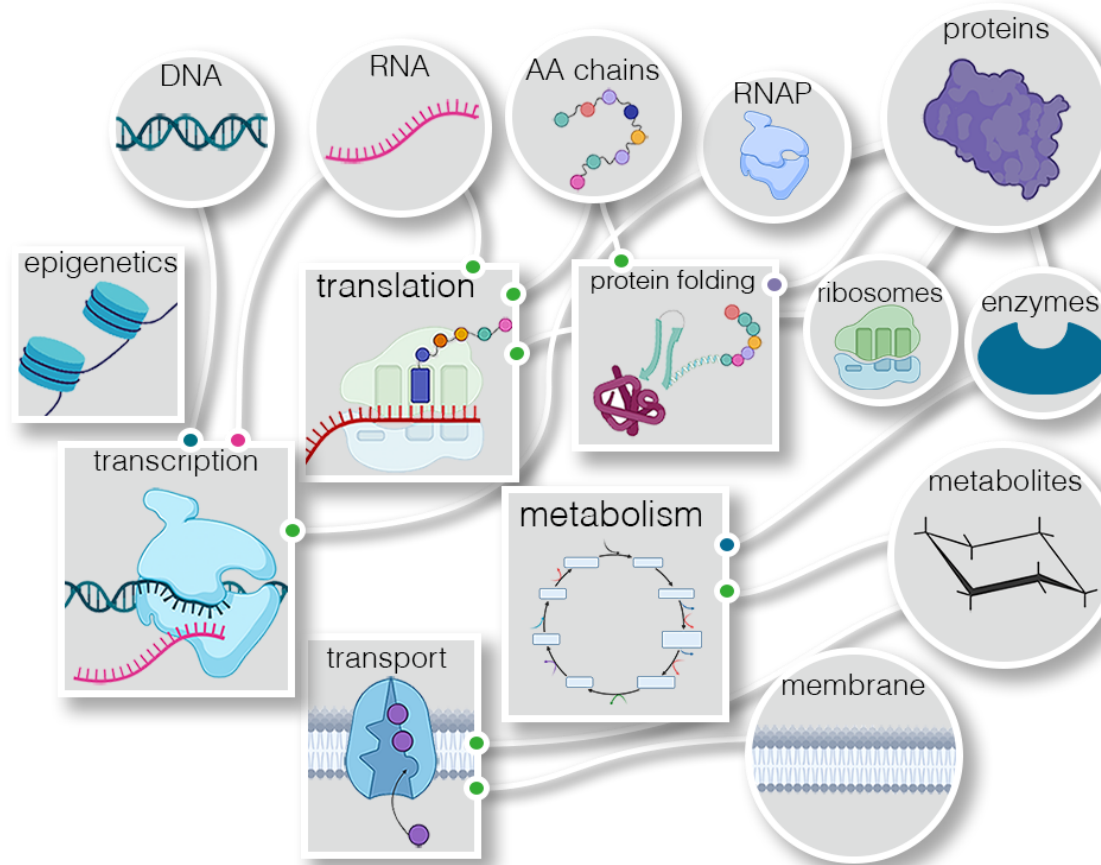


Composition requires explicit coupling

Whereas traditional systems biology models focus on the structure or dynamics of specific subsystems in controlled conditions...

Compositional systems biology aims to connect these models, asking questions about the *space between models*.

- What variables should a submodel expose through its interface?
- **How do coupled models connect?**

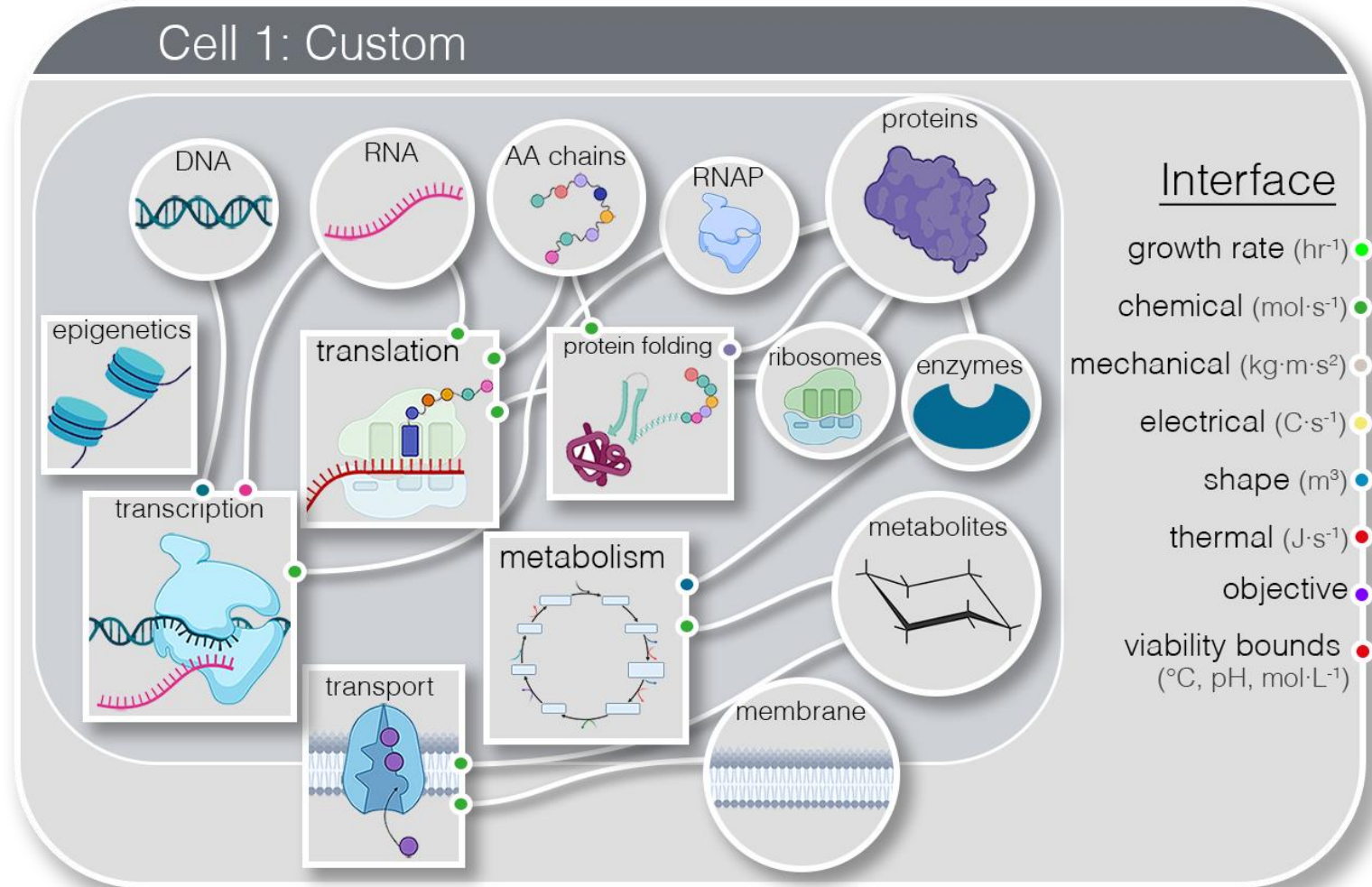


Composition requires translation across scales

Whereas traditional systems biology models focus on the structure or dynamics of specific subsystems in controlled conditions...

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- What variables should a submodel expose through its interface?
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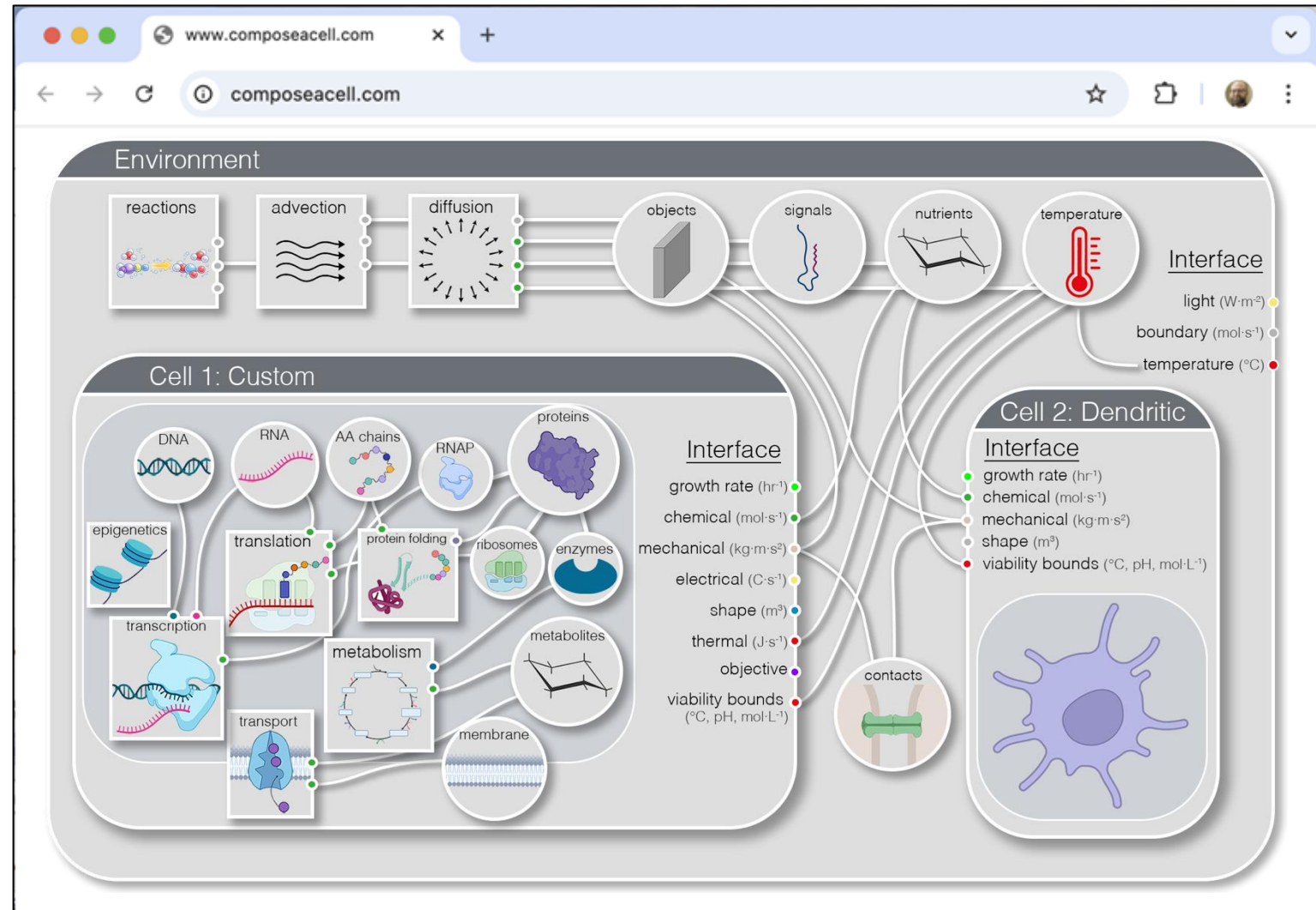


The real challenge is community composition

Whereas traditional systems biology models focus on the structure or dynamics of specific subsystems in controlled conditions...

Compositional systems biology aims to connect these models, asking questions about the *space between models*.

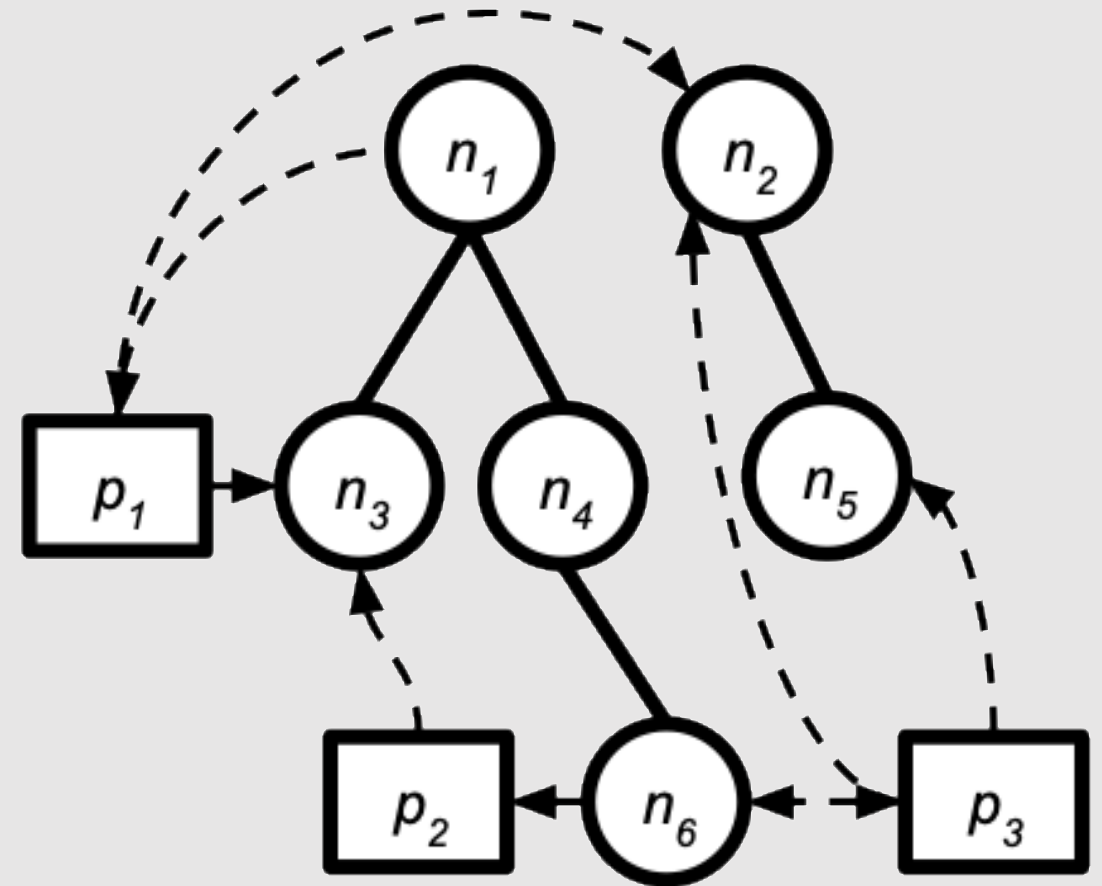
- What variables should a submodel expose through its interface?
- How do coupled models connect?
- How do models translate across scales?
- **Can we build infrastructure for the open-ended composition of multiscale models by a community of researchers?**



Process Bigraph provides a composition language. Vivarium executes it

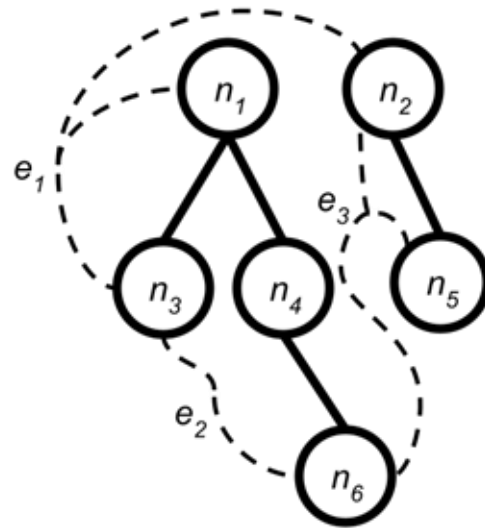
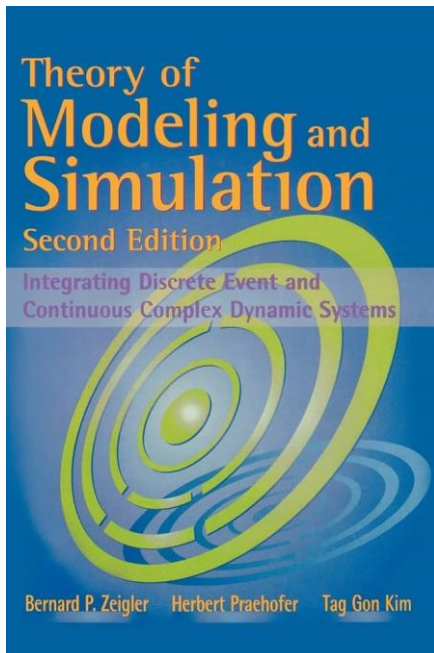
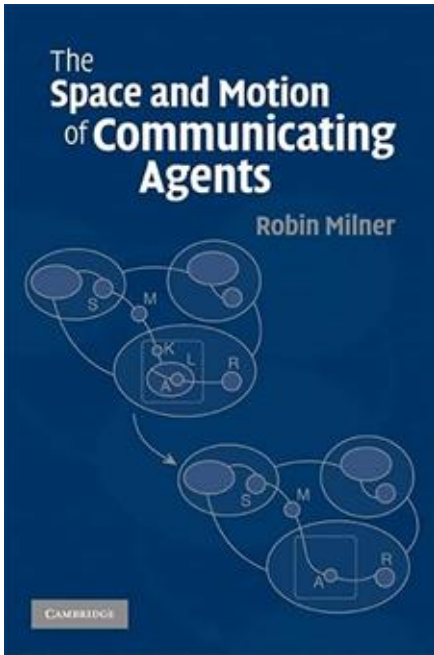
Process bigraph is a meta-framework that provides a typed, executable “composition language” for wiring heterogeneous models across scales.

Vivarium is the software – an engine that runs process bigraph specifications



Milner Bigraphs meet Discrete Event Simulation

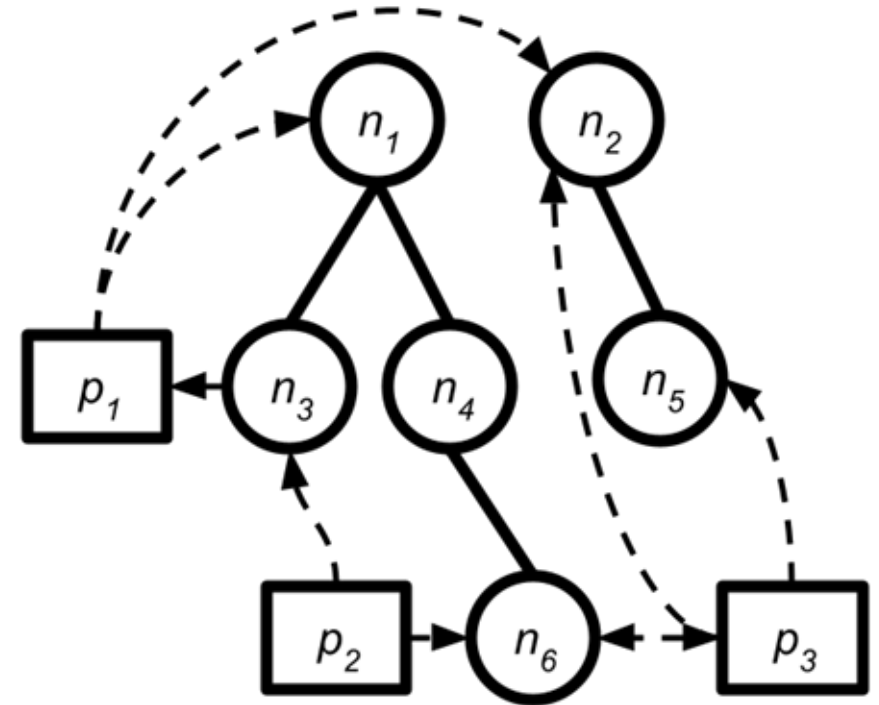
Process bigraphs turn model wiring into an executable graph



Milner bigraph



Discrete Event System specification (DEVS)



process bigraph

Bigraphs: Milner, Robin. "The space and motion of communicating agents." Cambridge University Press (2009)

DEVS: Zeigler, Bernard P., Praehofer, H., & Kim, T.G "Theory of modeling and simulation". Academic press (2000).

Process Bigraphs: Agmon, E. et al. "Vivarium: an interface and engine for integrative multiscale modeling in computational biology." Bioinformatics (2022)

Agmon, E. & Spangler, R.K. "Process Bigraphs and the Architecture of Compositional Systems Biology." arXiv (2025).

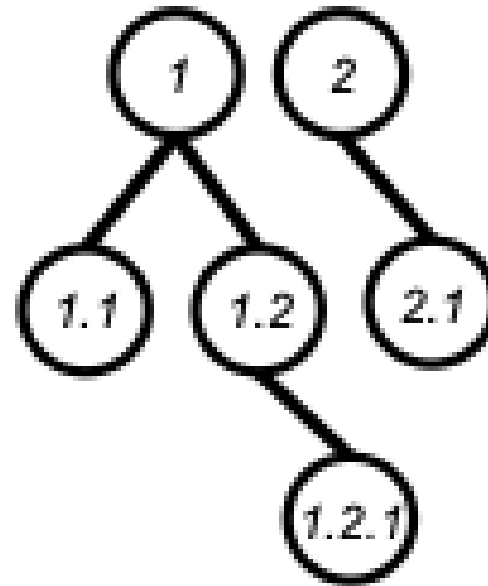
Stores

Typed state across nested place graphs – can hold any data type, from scalars to novel structures

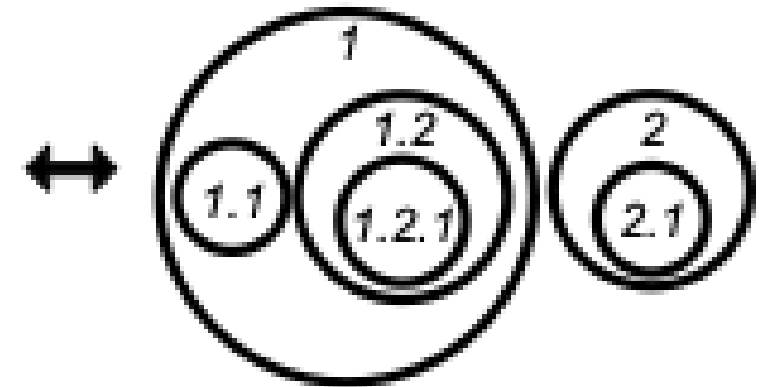
single store



place graph

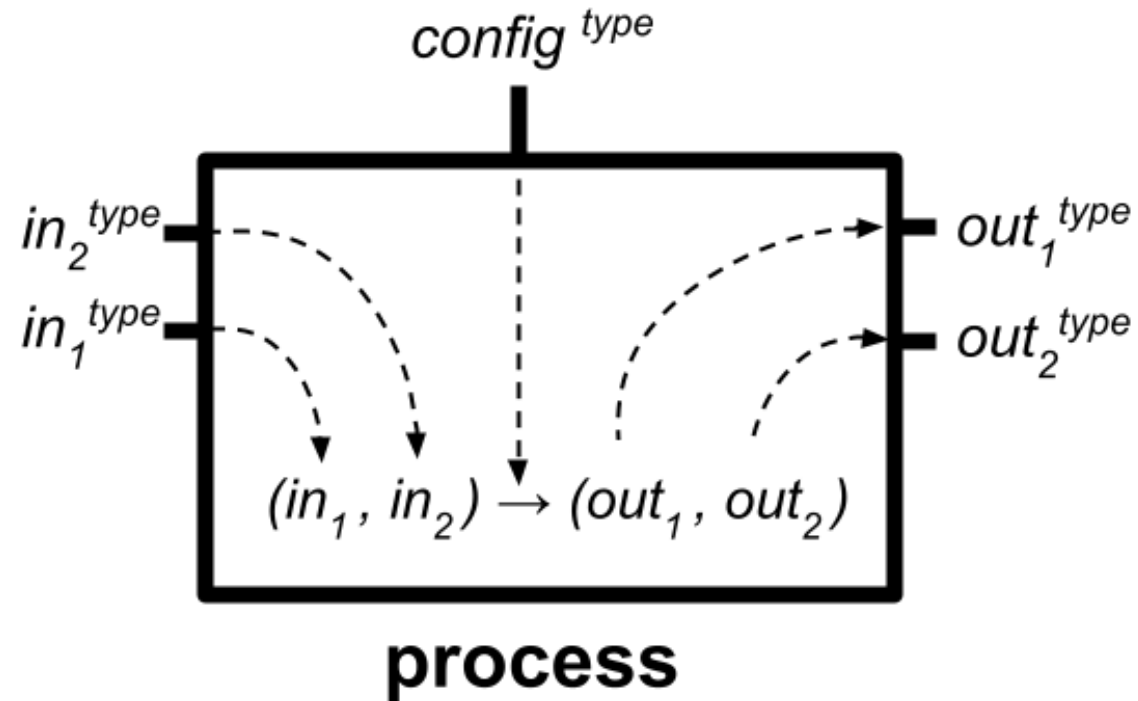


nested view



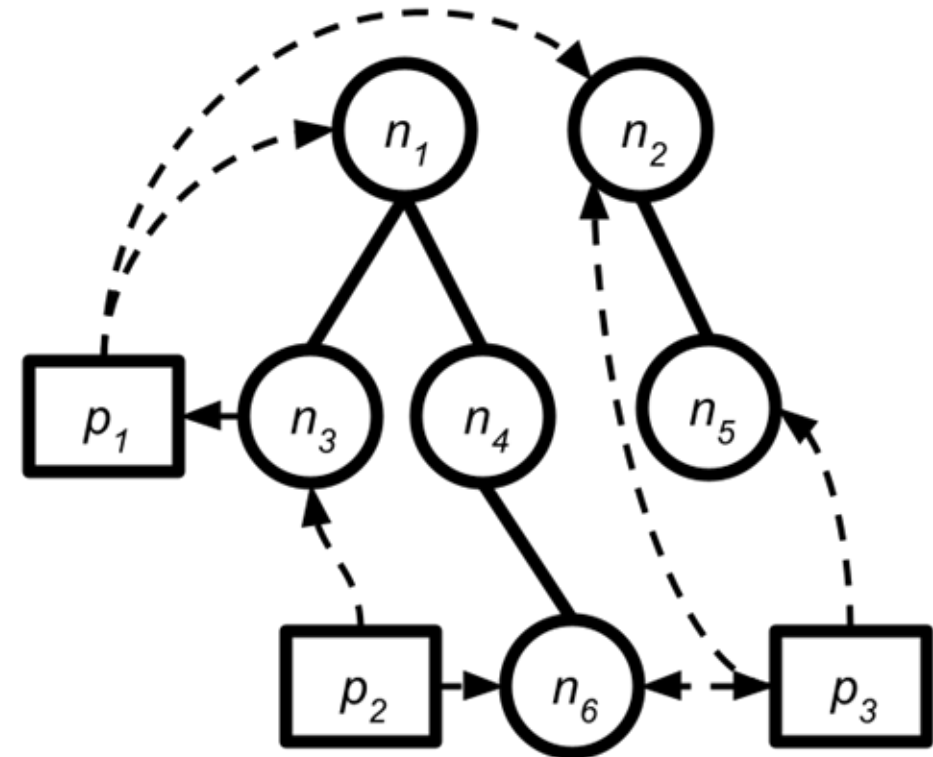
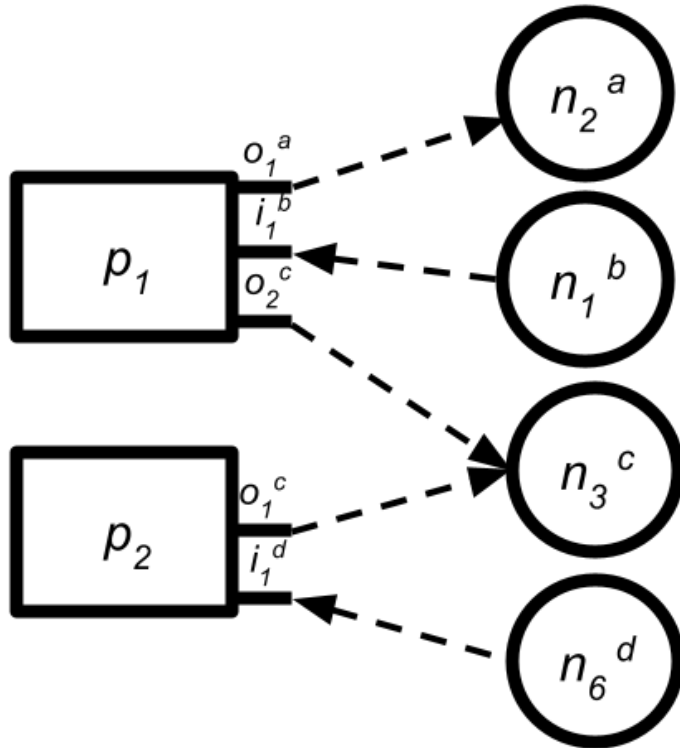
Processes

Callable mechanisms: typed state-in $\rightarrow$ typed updates-out, config to parameterize



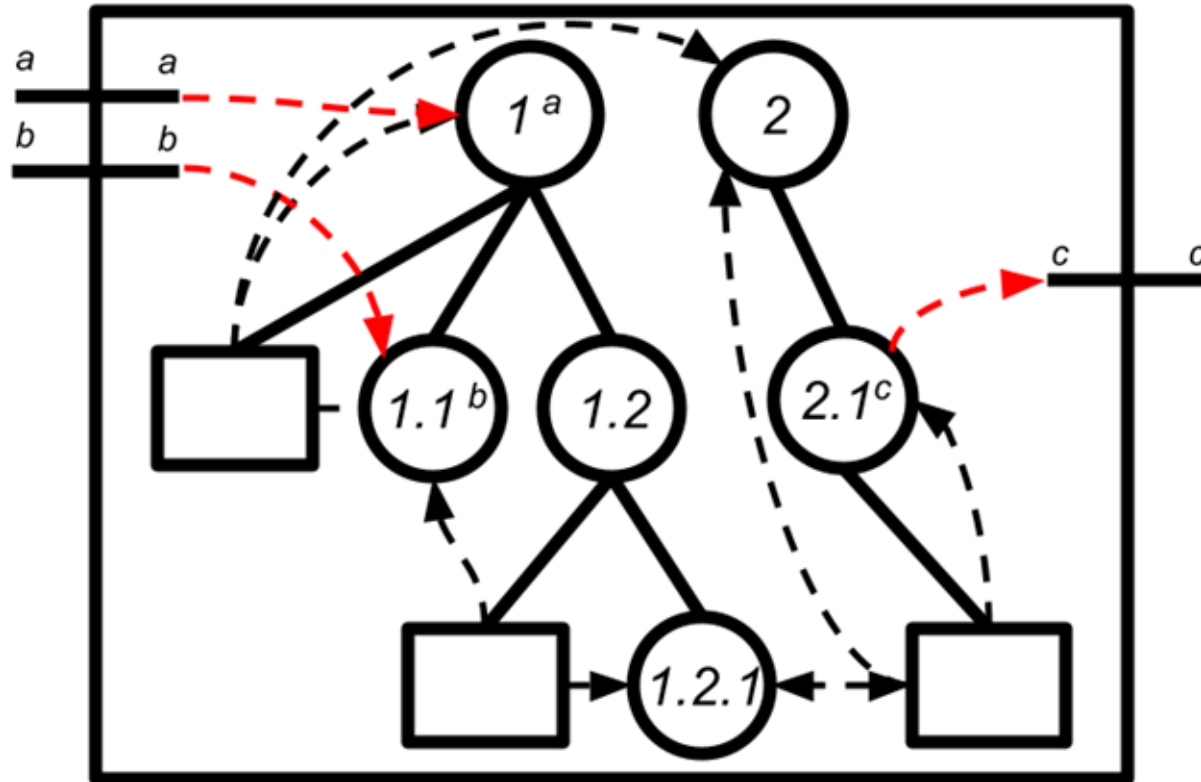
Composites

Wire processes to stores: executable model graphs



Composite Process

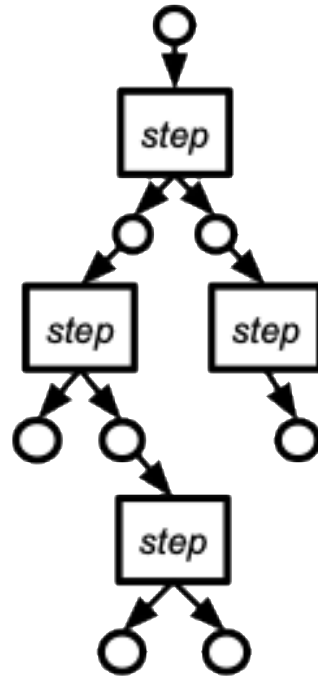
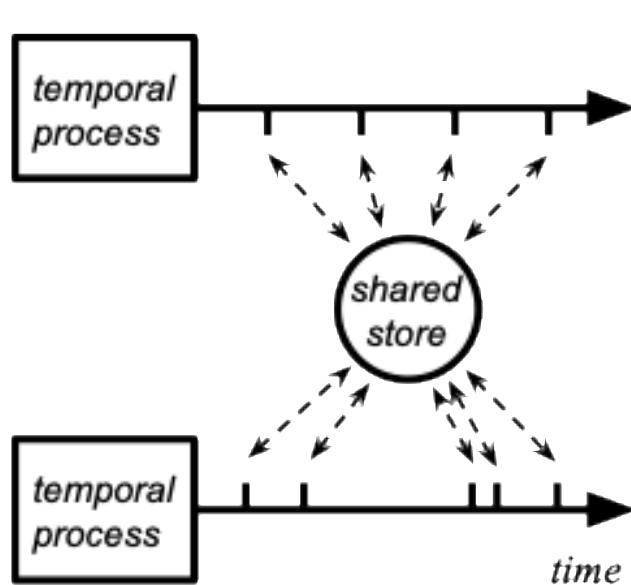
Encapsulated subgraph with a clean interface



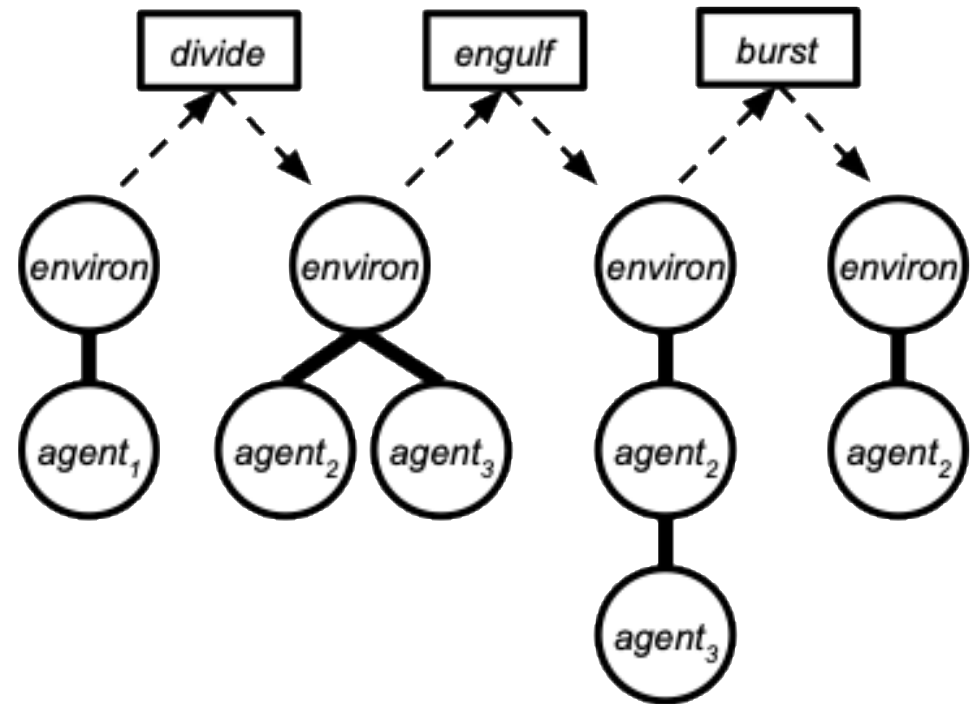
Orchestration Patterns

Scheduling templates for coordination of processes.

discrete event co-simulation workflow



event-driven graph rewrite



Term	Formal anchor	Description
Paths, types, and values	P paths, T types, and V values	These are the ingredients needed to name locations in a hierarchical system, declare what may be stored there, and assign concrete values.
Schema	$\Sigma : P \rightarrow T$	The schema is the typed organizational blueprint of the system.
State and stores	$x : P \rightarrow V$	The state assigns values to schema paths, and stores are the state locations that function as shared variables.
Process	$f : (in_{\tau_1}, \dots) \rightarrow (out_{\tau_2}, \dots)$	A process is a mechanism with an interface, defined by what it reads, what it can update, and its configuration.
Deltas and typed application	$\delta = update(x_{in}, \Delta t)$ and $x' = apply_{\tau}(x, \delta)$	Processes emit typed updates rather than directly overwriting state, and each type determines how its updates are applied.
Ports and wiring	$W : (\text{process}, \text{port}) \rightarrow P$	Ports specify accessible variables, and wiring makes every coupling explicit by mapping each port to the state path it reads or writes.
Type registry	R_T	The type registry defines available types and their validation and update semantics, including the operator $apply_{\tau}$.
Link registry	R_L	The link registry maps process addresses to concrete handler classes, connecting abstract process nodes to executable implementations.
Process bigraph	$B = (\Sigma, x, R_T, R_L)$	A process bigraph is the typed and executable organization as a whole, with its wiring pattern derived from the port bindings stored in the state.
Composite and bridge	$bridge : (\text{external port}) \rightarrow P$	A composite packages an internal process bigraph as a single higher-level process and maps its external interface onto internal state paths.
Orchestration	$\langle B, t, t_{next} \rangle \rightarrow \langle B', t', t'_{next} \rangle$	Orchestration specifies when processes run, how their deltas are combined, and how structural rewrites are incorporated over time.

Table 1. Core vocabulary of Process Bigraph. Detailed definitions are provided in the Supplementary Materials.

(This is not just a diagramming convention; it is an executable formal structure)

Vivarium Collective software ecosystem example libraries:

- **bigraph-schema** — Type system for hierarchical model state, validation, and update semantics.
- **process-bigraph** — Execution engine for typed processes, composites, wiring, and orchestration.
- **bigraph-viz** — Graph visualization for process-bigraph structures.
- **viva-superpowers** — AI workflow tools for wrapping simulators, composing models, and generating reports.
- **spatio-flux** — reference example composing metabolism, fields, and particles.
- Approximately ~30 stand-alone applications of this software

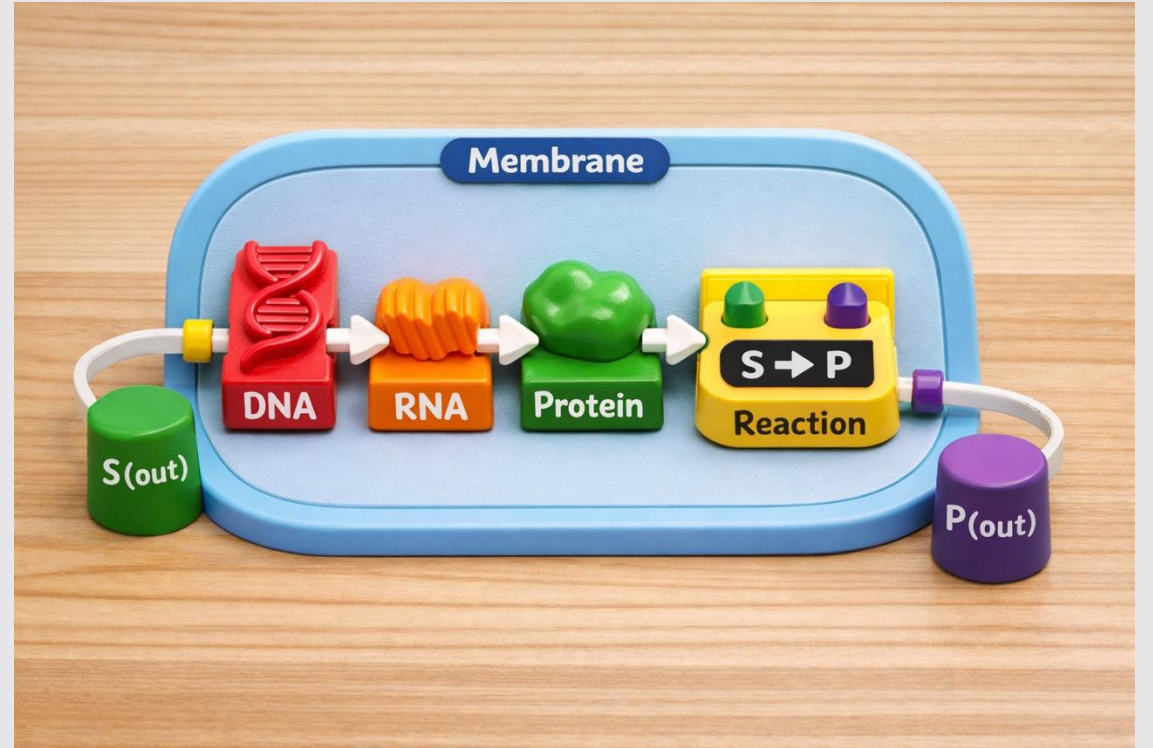
GitHub: github.com/vivarium-collective

(and it is instantiated in a rich software ecosystem)

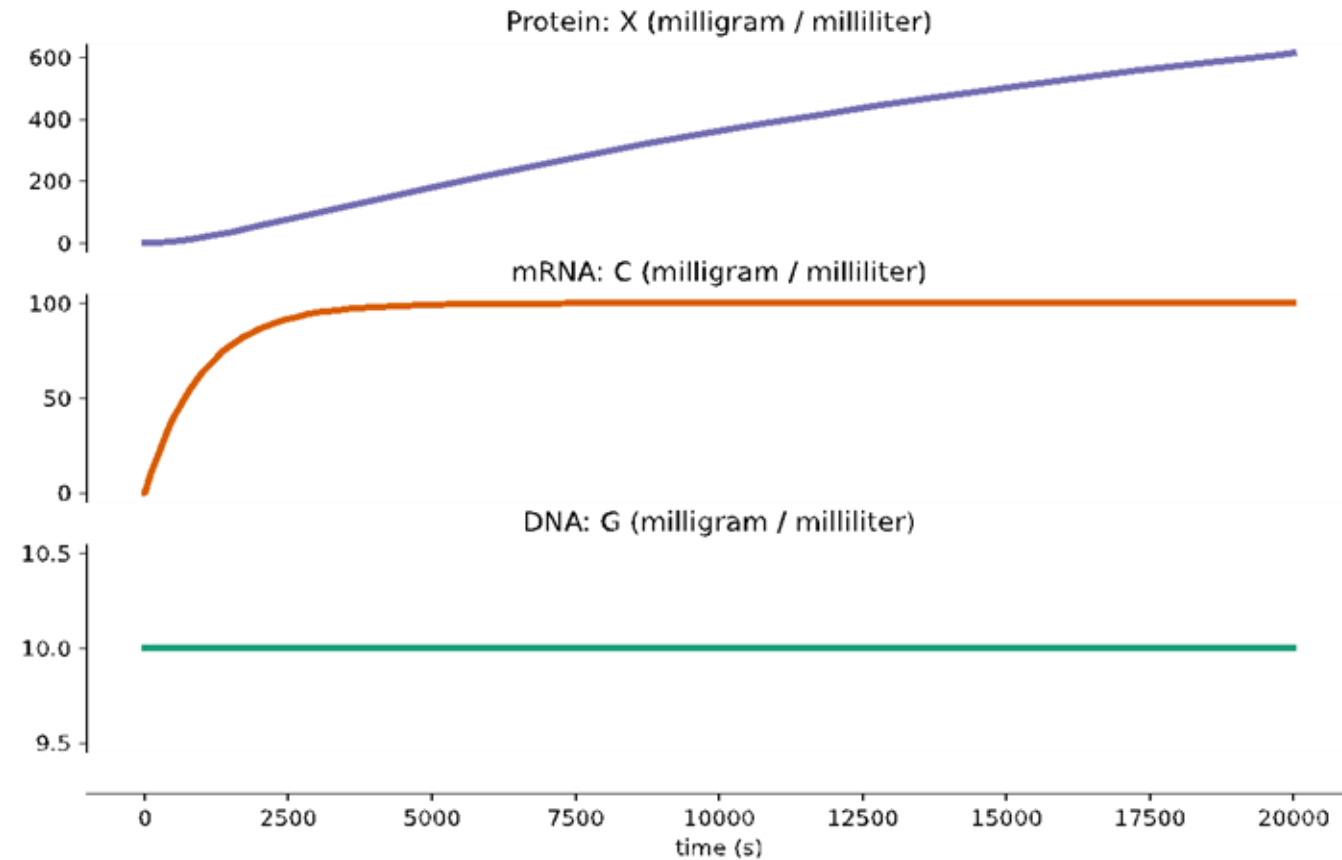
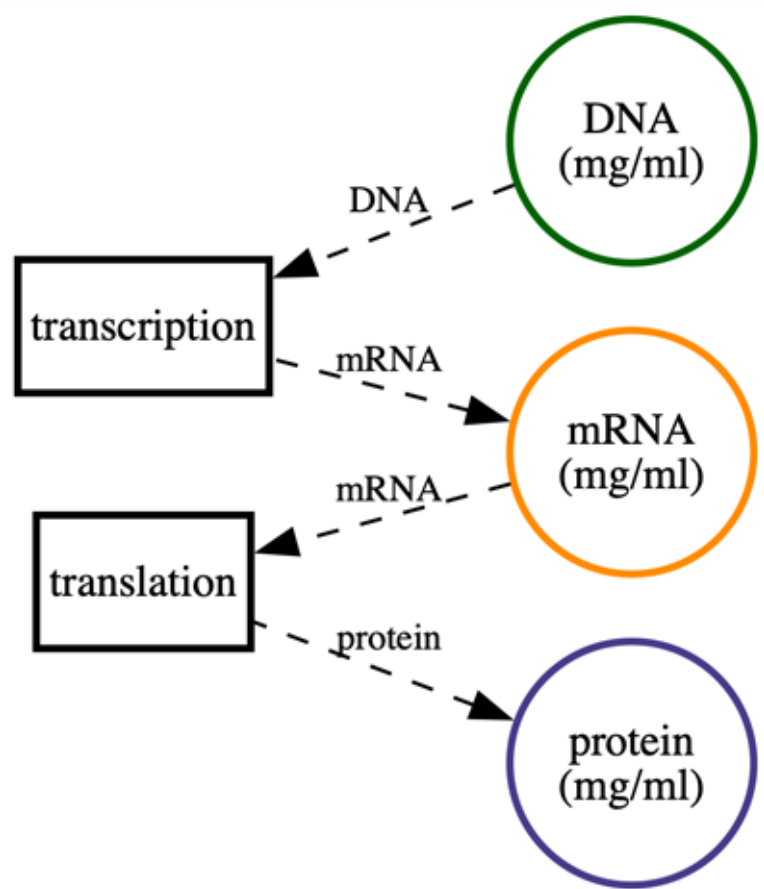
Full supplement with formal definitions:



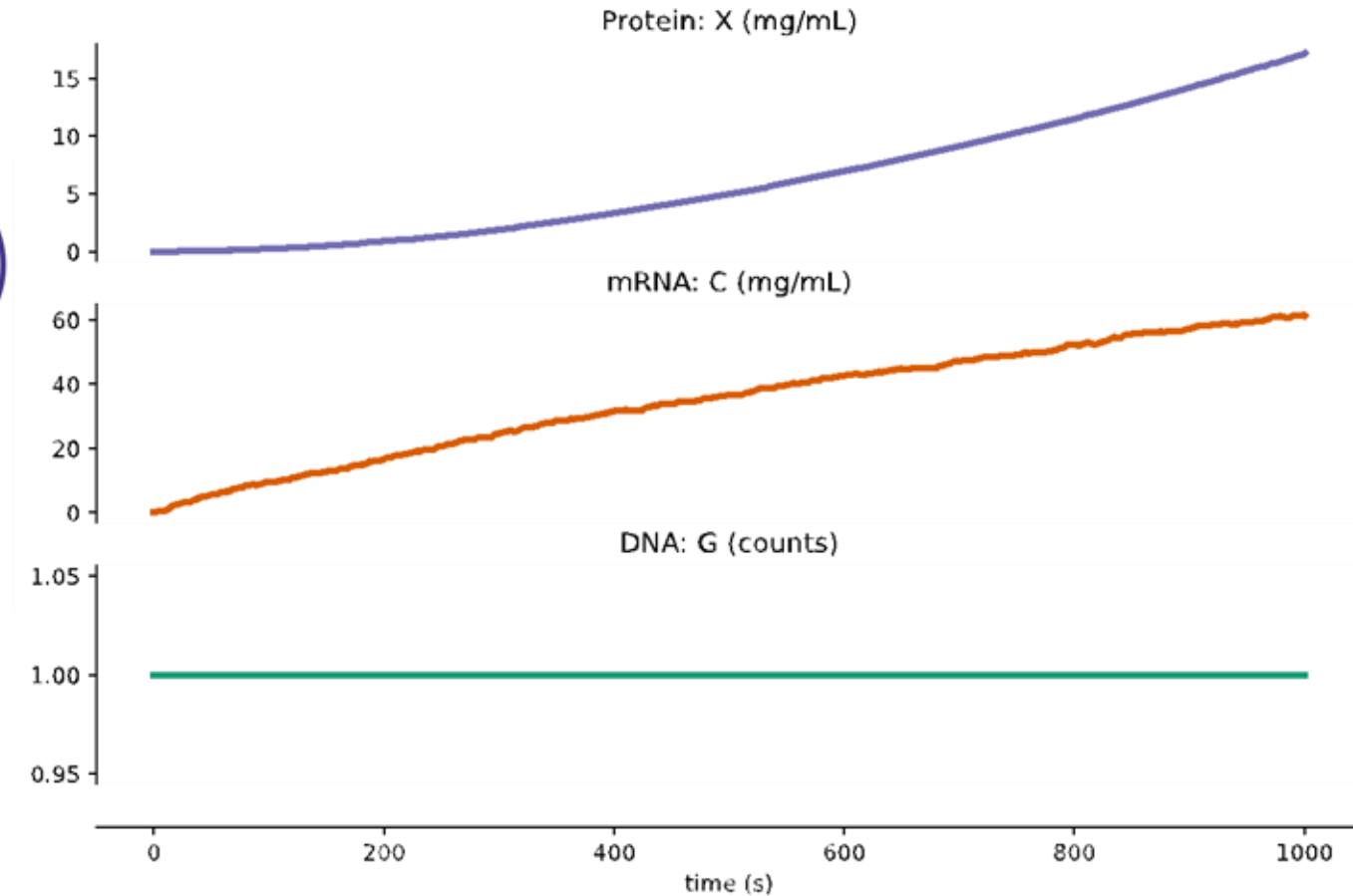
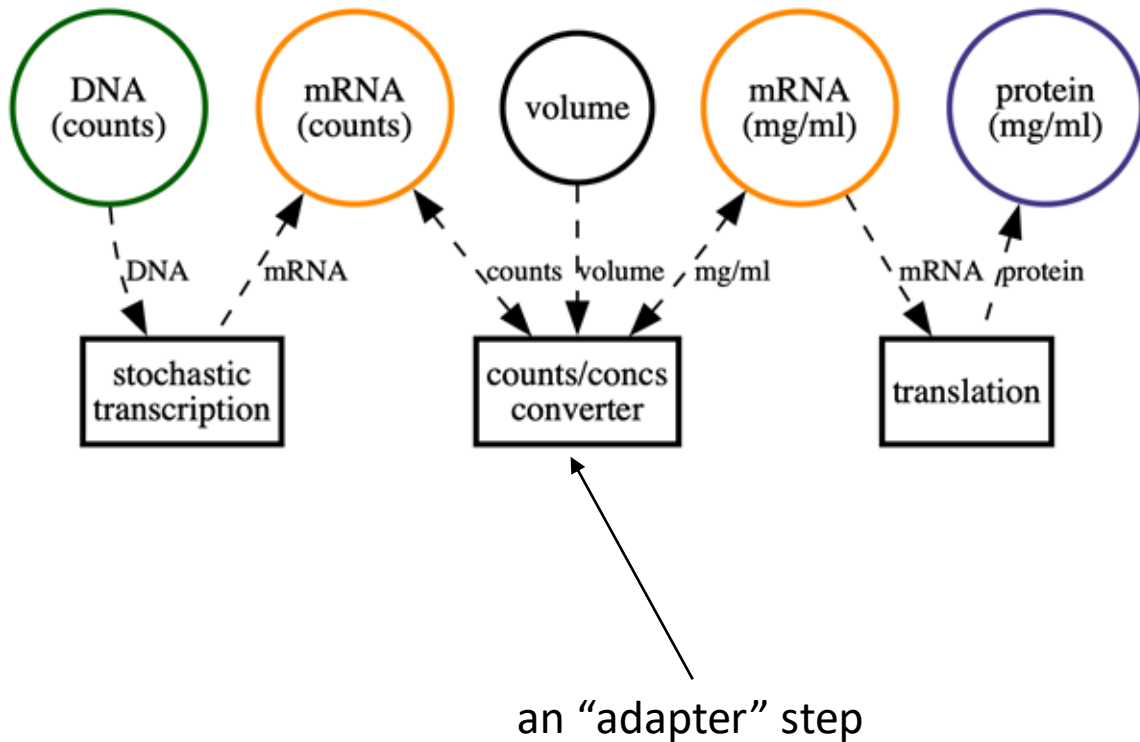
A Minimal Example for Building Intuition



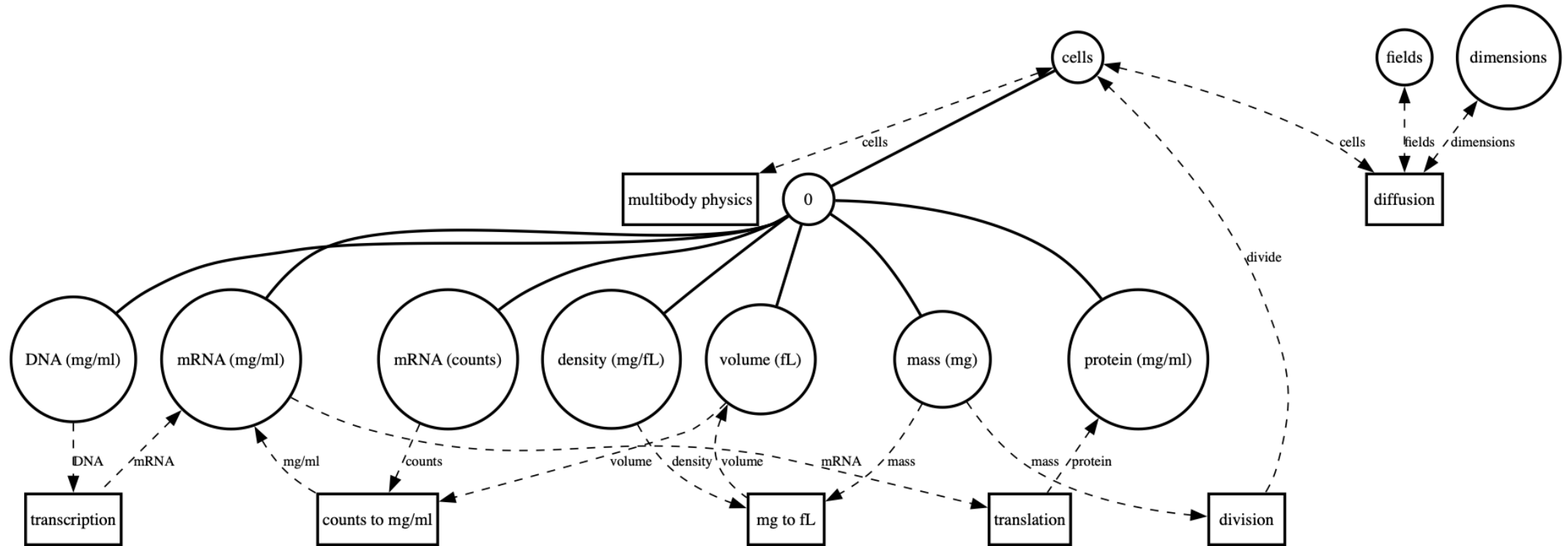
Minimal Composite: Transcription + Translation



Multi-timestepping enables stochastic/deterministic hybrid simulation



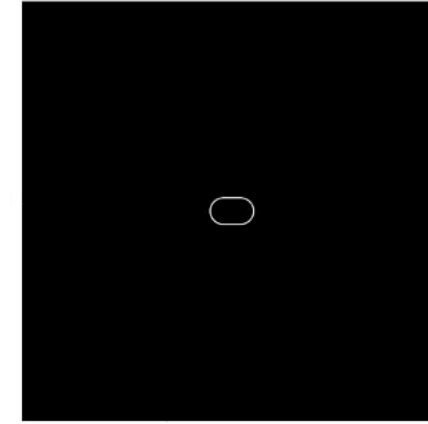
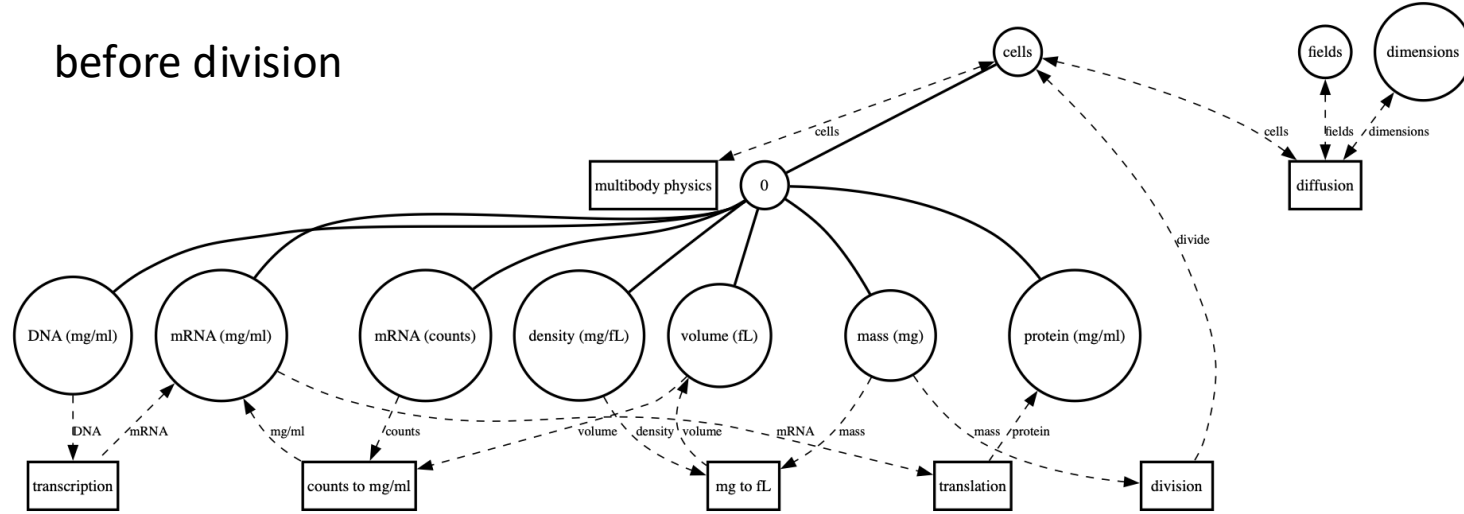
Hierarchical nesting enables multiple spatial scales



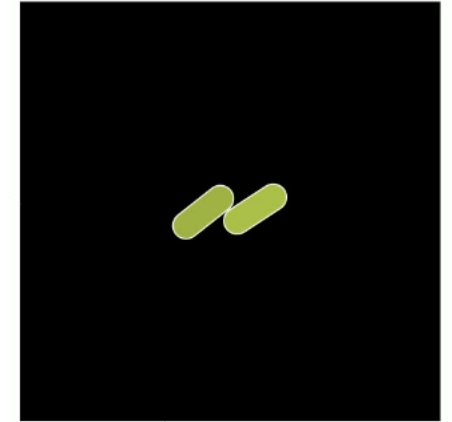
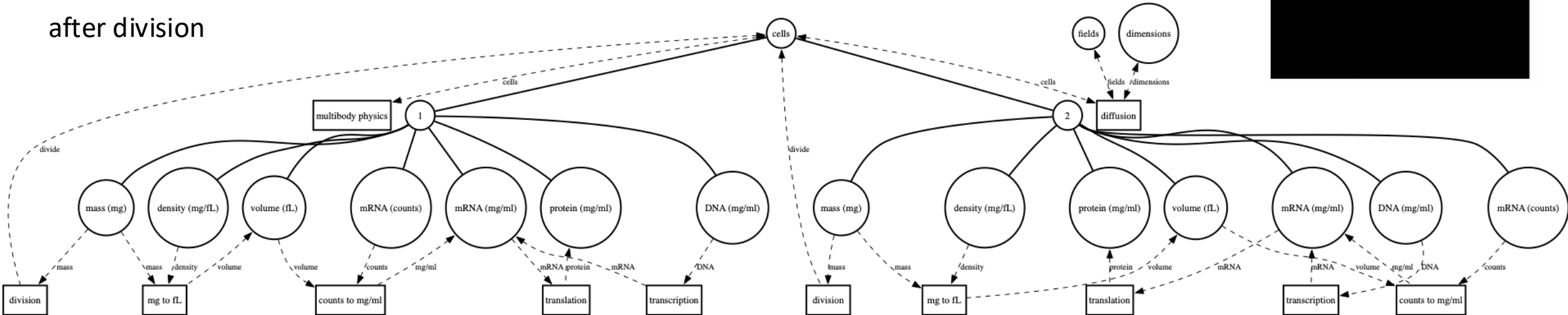
Event-drive graph rewrite example: division

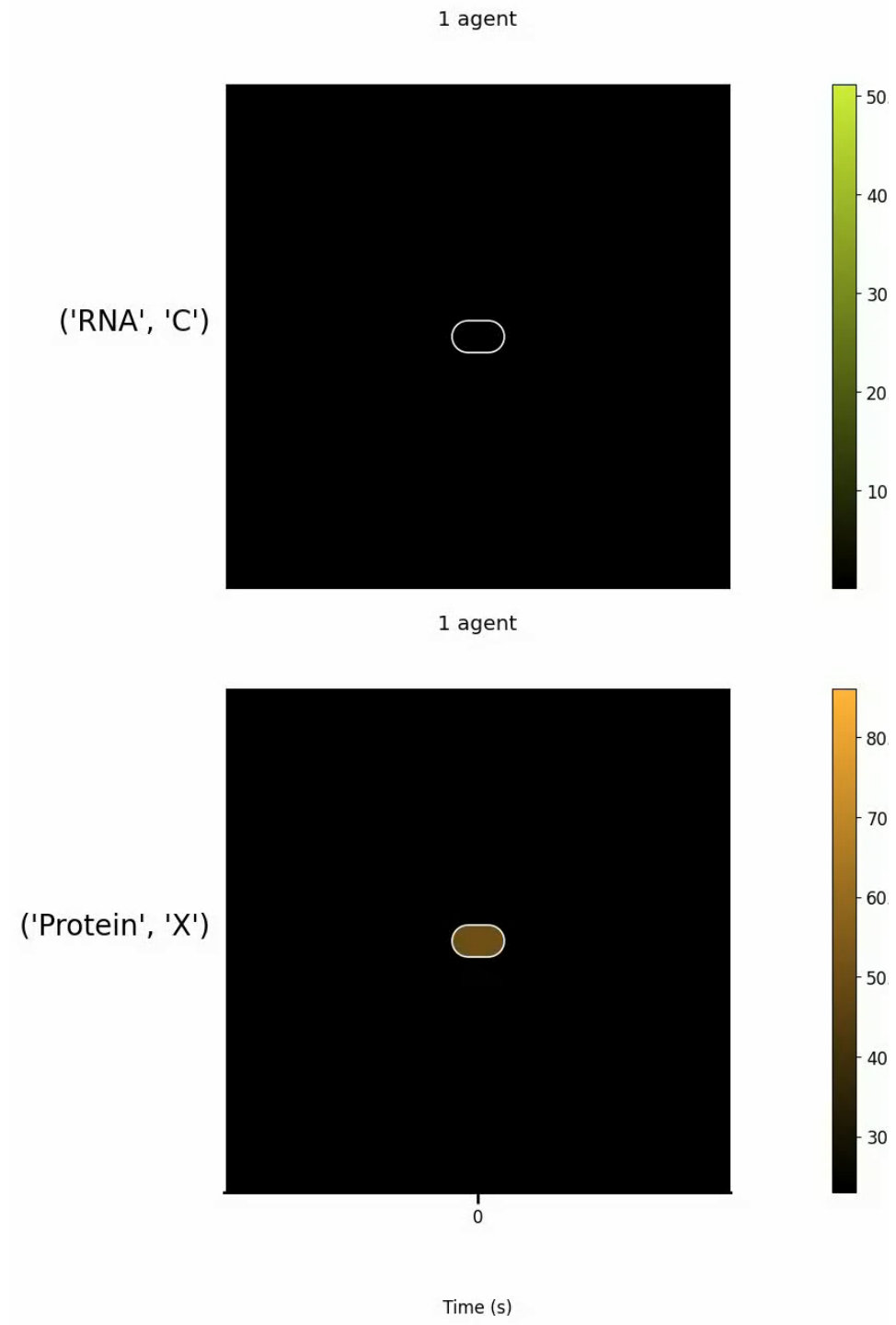
sub-graphs can be added/removed/moved during simulation runtime

before division



after division





Vivarium Workbench

A new browser-based GUI for organizing Vivarium projects

 Vivarium workbench

- biomodels main

WORKSPACE

- Sources
- Registry
- Composites
- Investigations
- Simulations DB
- Analyses

STUDIES

No studies yet

pbjg-biomodels-bundle

Regression harness for BioModels: runs each model under multiple simulators (COPASI, Tellurium) and renders an interactiv...
Source: <https://github.com/vivarium-collective/pbg-biomodels-bundle.git> @ main

unmanaged

pbjg-bioreactordesign

Process-bigraph wrapper for BioReactorDesign (BiRD) bioreactor simulation
Source: <https://github.com/vivarium-collective/pbg-bioreactordesign.git> @ main
Path: /Users/eranagmon/code/pbg-bioreactordesign

installed

pbjg-caspule

Process-bigraph wrapper for CASPULE (a LAMMPS variant with dynamic bond formation/breaking)
Source: <https://github.com/vivarium-collective/pbg-caspule.git> @ main
Path: /Users/eranagmon/code/pbg-caspule

installed

pbjg-cellpack

Process-bigraph wrapper for cellPACK — mesoscale molecular packing (recipes → 3D molecular assemblies)
Source: <https://github.com/vivarium-collective/pbg-cellpack.git> @ main
Path: /Users/eranagmon/code/pbg-cellpack

installed

pbjg-comets

Process-bigraph wrapper for COMETS (dynamic FBA + 2D spatial microbial ecosystems)
Source: <https://github.com/vivarium-collective/pbg-comets.git> @ main
Path: /Users/eranagmon/code/pbg-comets

installed

pbjg-composite-nfsim-caspule

Process-bigraph composite: CASPULE bond-aware MD coupled to NFSim rule-based kinetics through a configurable...
Source: <https://github.com/vivarium-collective/pbg-composite-nfsim-caspule.git> @ main

unmanaged

pbjg-compuCell3d

Process-bigraph wrapper for the CompuCell3D multicellular simulation environment
Source: <https://github.com/vivarium-collective/pbg-compuCell3d.git> @ main
Path: /Users/eranagmon/code/pbg-compuCell3d

installed

pbjg-copasi

process-bigraph-compatible COPASI Steps and Processes for SBML simulation
Source: <https://github.com/vivarium-collective/pbg-copasi.git> @ main

via pyproject

pbjg-emitters

Focused emitter library for process-bigraph composites
Source: <https://github.com/vivarium-collective/pbg-emitters.git> @ main

via pbg-superpowers

pbjg-lammps

Process-bigraph wrapper for the LAMMPS molecular dynamics simulator
Source: <https://github.com/vivarium-collective/pbg-lammps.git> @ main
Path: /Users/eranagmon/code/pbg-lammps

installed

pbjg-martini

Process-bigraph wrapper for the Martini coarse-grained force field — membrane systems, micelles, protein-lipid complexes, and vesicles
Source: <https://github.com/vivarium-collective/pbg-martini.git> @ main
Path: /Users/eranagmon/code/pbg-martini

installed

pbjg-medyan

Process-bigraph wrapper for the MEDYAN cytoskeleton simulator: pure-Python re-implementation + a subprocess-driven bridge to the real ME...
Source: <https://github.com/vivarium-collective/pbg-medyan.git> @ main
Path: /Users/eranagmon/code/pbg-medyan

installed

pbjg-mem3dg

Process-bigraph wrapper for Mem3DG membrane mechanics simulator
Source: <https://github.com/vivarium-collective/pbg-mem3dg.git> @ main
Path: /Users/eranagmon/code/pbg-mem3dg

installed

pbjg-membrane-actin-composite

Process-bigraph composite: pbg-mem3dg + pbg-readdy as a Brownian ratchet (actin pushing on membrane, closed-loop)
Source: <https://github.com/vivarium-collective/pbg-membrane-actin-composite.git> @ main
Path: /Users/eranagmon/code/pbg-membrane-actin-composite

installed

pbjg-nfsim

A process-bigraph wrapper for BioNetGen/NFSim
Source: <https://github.com/vivarium-collective/pbg-nfsim.git> @ main

via pbg-composite-nfsim-caspule

pbjg-reactive-system

Process-bigraph wrapper for Milner-style Bigrphical Reactive Systems, with a worked MAPK signalling example.
Source: <https://github.com/vivarium-collective/pbg-reactive-system.git> @ main
Path: /Users/eranagmon/code/pbg-reactive-system

installed

pbjg-readdy

Process-bigraph wrapper for the ReaDDy particle-based reaction-diffusion simulator
Source: <https://github.com/vivarium-collective/pbg-readdy.git> @ main
Path: /Users/eranagmon/code/pbg-readdy

installed

<https://github.com/vivarium-collective/vivarium-workbench>

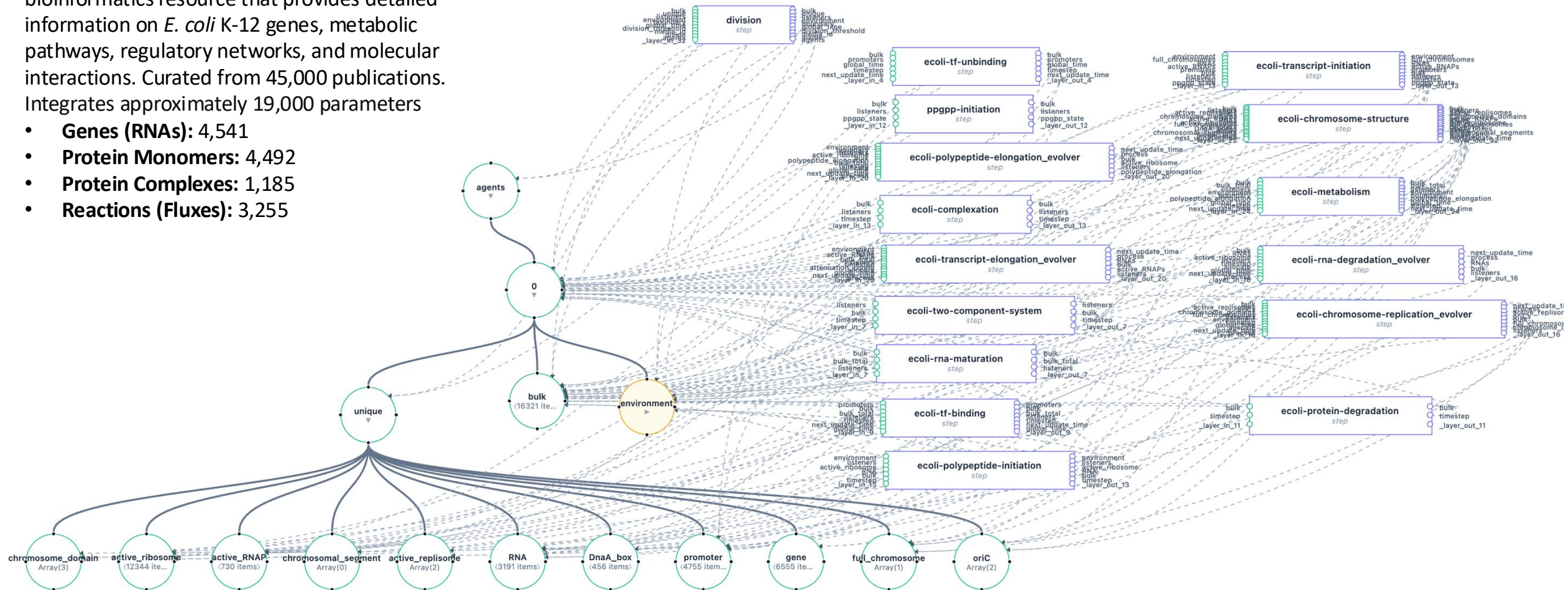
Flagship application: Whole-Cell *E. coli*

E. coli WCM
demo:

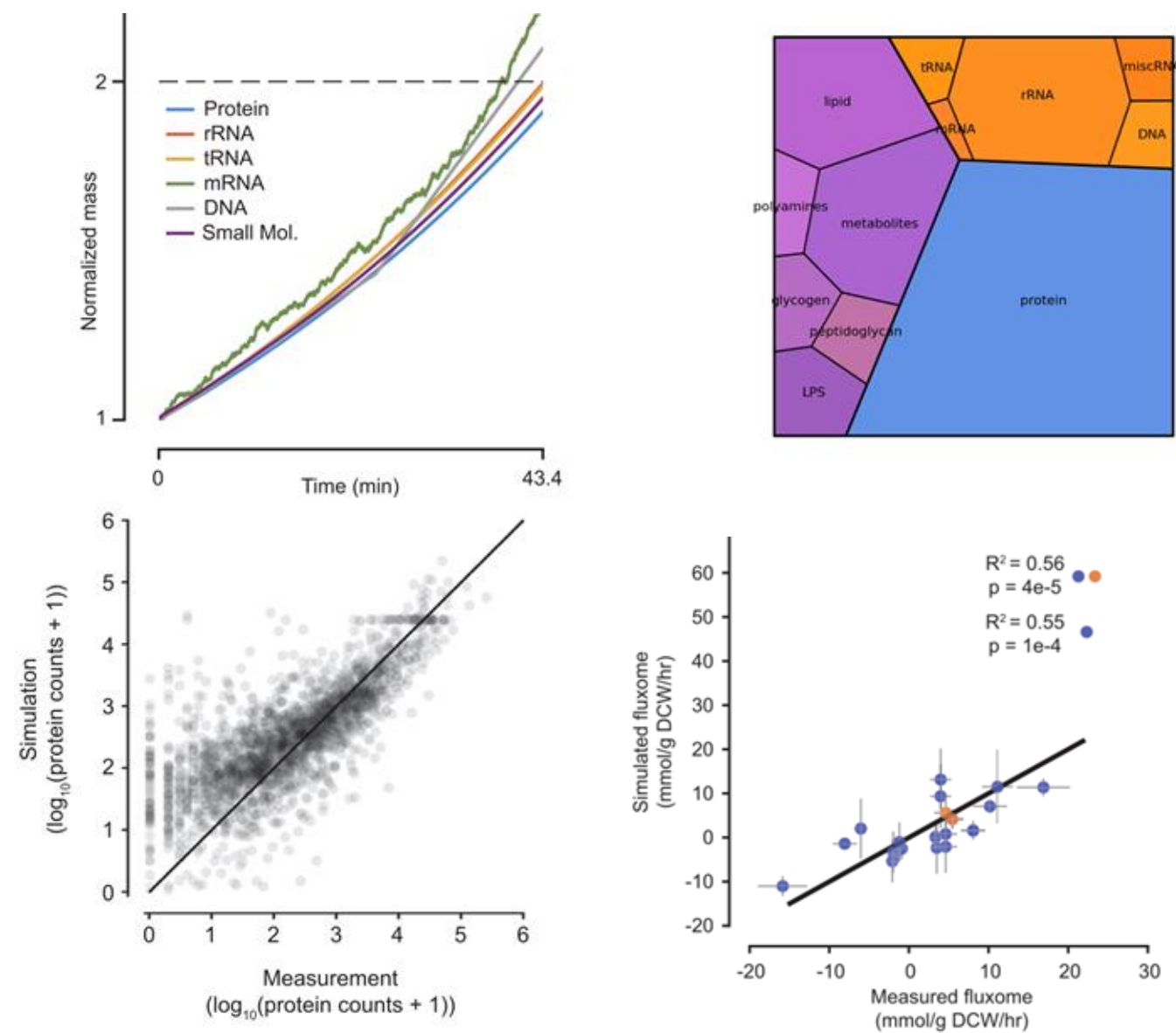


Pipeline from EcoCyc: a curated database and bioinformatics resource that provides detailed information on *E. coli* K-12 genes, metabolic pathways, regulatory networks, and molecular interactions. Curated from 45,000 publications. Integrates approximately 19,000 parameters

- **Genes (RNAs):** 4,541
- **Protein Monomers:** 4,492
- **Protein Complexes:** 1,185
- **Reactions (Fluxes):** 3,255



Whole-Cell *E. coli*



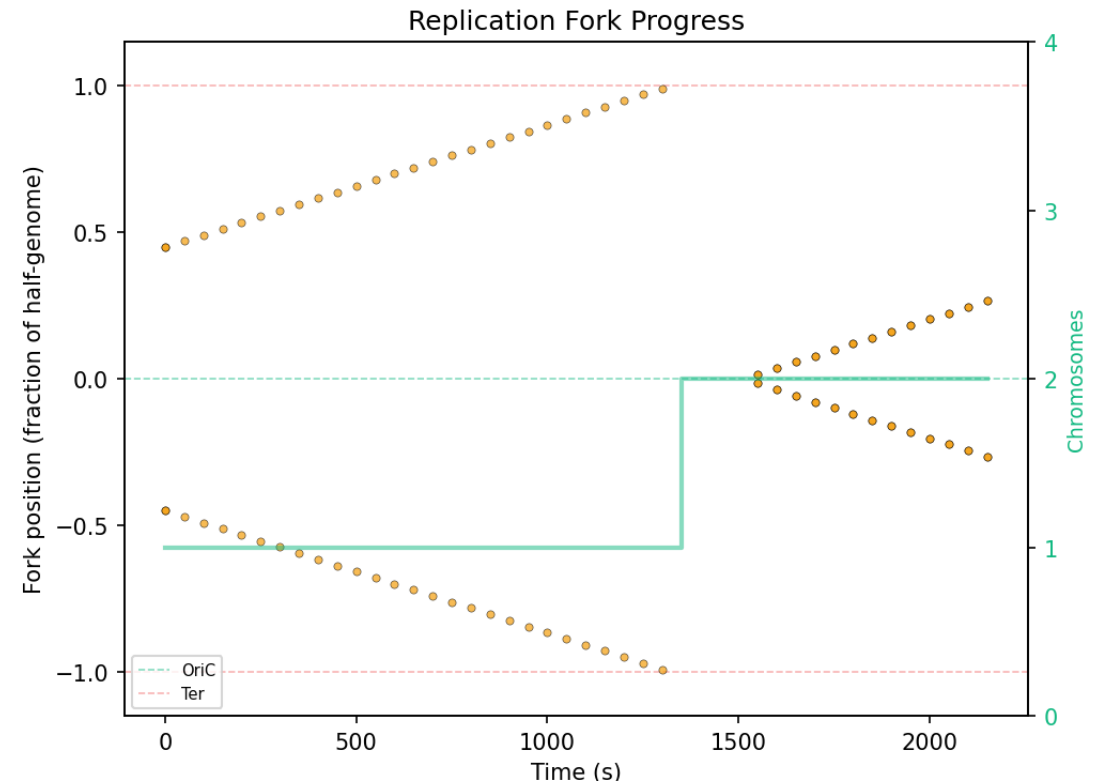
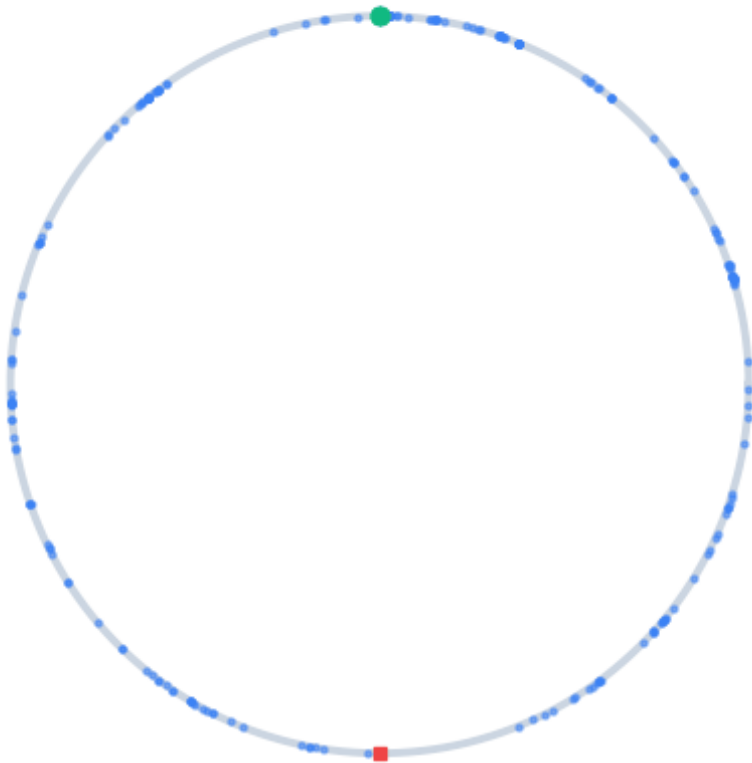
AB medium with 0.2% glucose

Cell Properties	
Simulation timesteps (1s each)	368,397
Doubling time (min)	47.97
Cell volume (fL)	1.06
Cell mass (fg)	1,167.63
Dry cell mass (fg)	350.50
Protein mass (fg)	152.60
RNA mass (fg)	46.77
DNA mass (fg)	6.18
Membrane mass (fg)	5.85
Small molecule mass (fg)	144.94
mRNA mass to total RNA mass	0.04
rRNA mass to total RNA mass	0.80
tRNA mass to total RNA mass	0.15
Ribosomal protein mass fraction	0.19

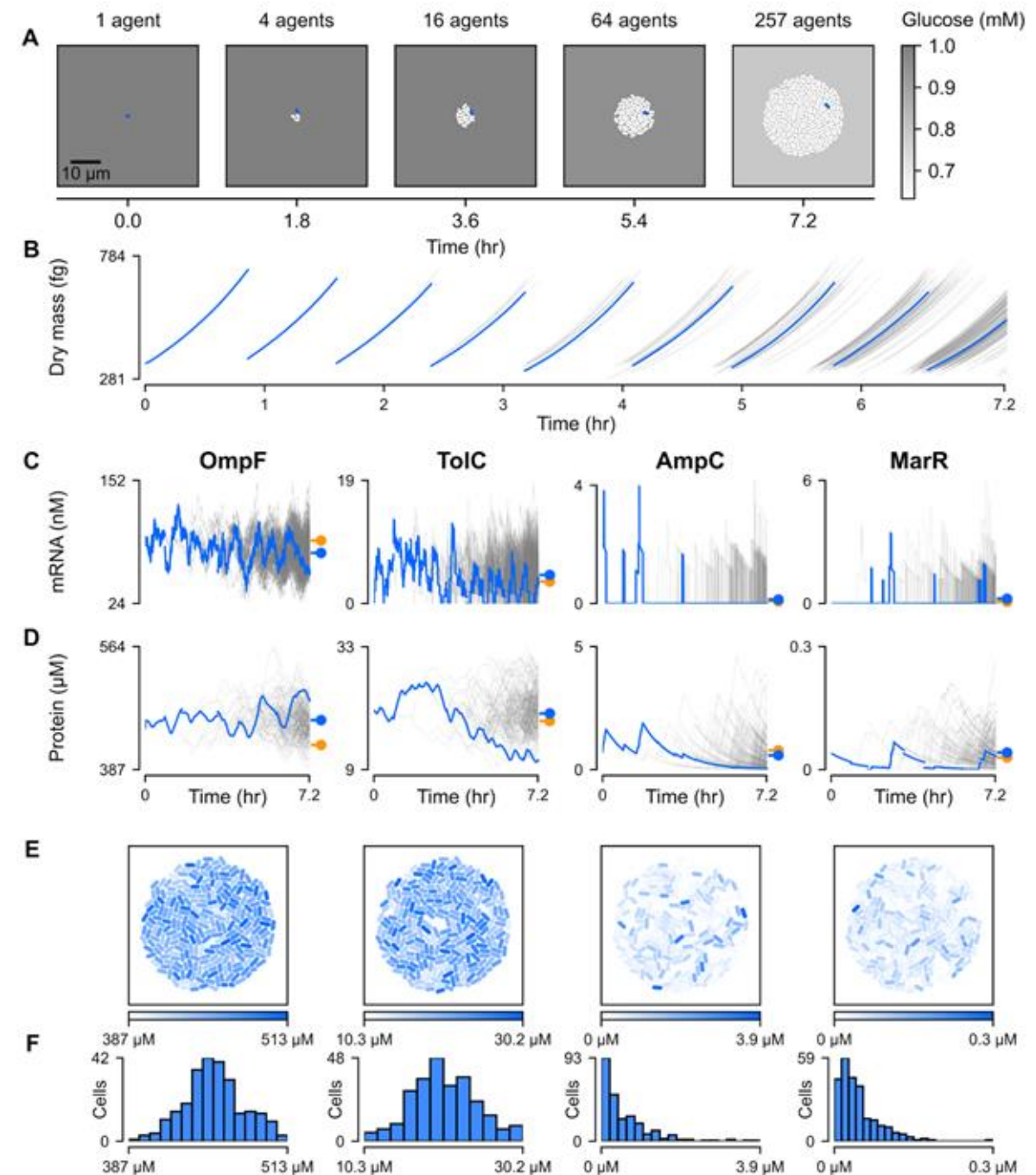
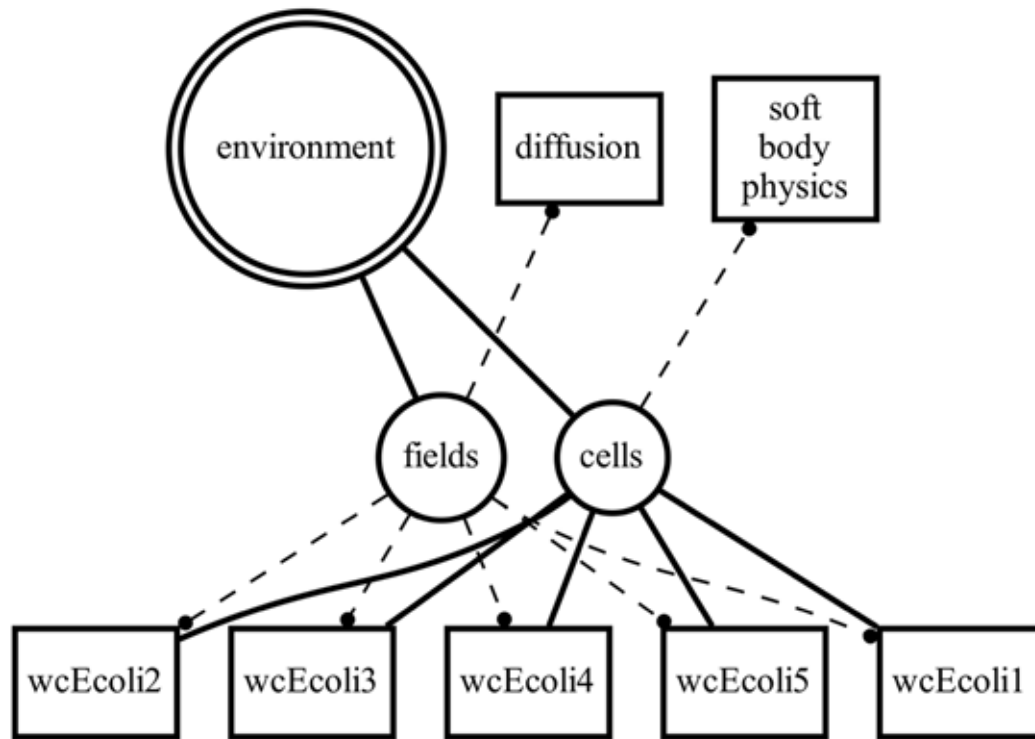
Whole-Cell *E. coli* Chromosome

t = 0 min · pre-initiation
forks 0 · RNAPs 248 · chromosomes 1

- OriC
- Ter
- ▶ RNAP
- ▲ Replisome

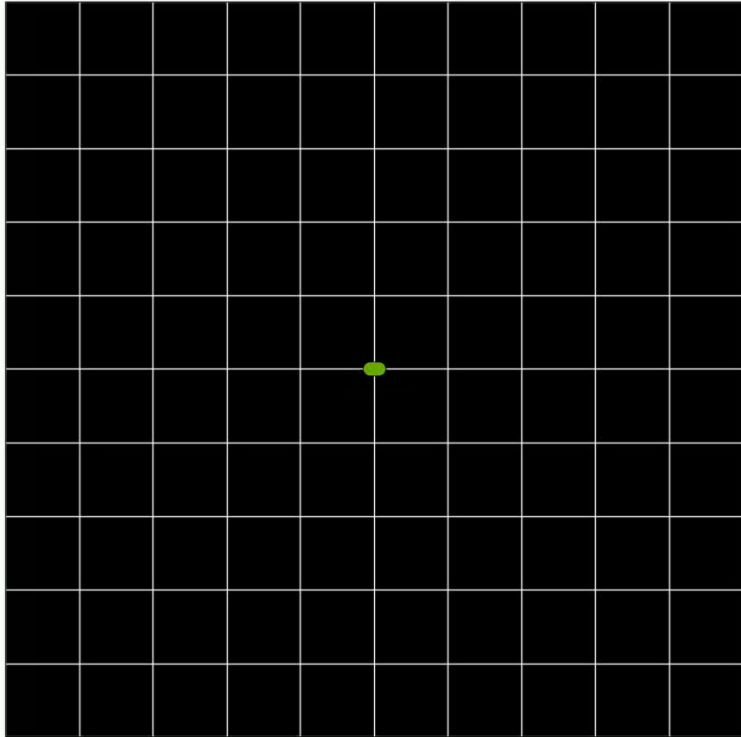


Whole-Cell *E. coli* colonies

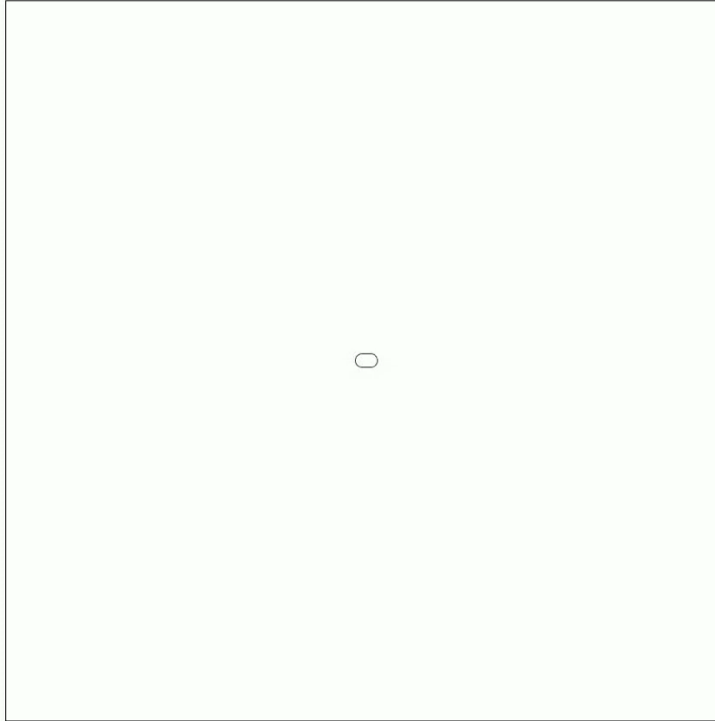


heterogeneous gene expression

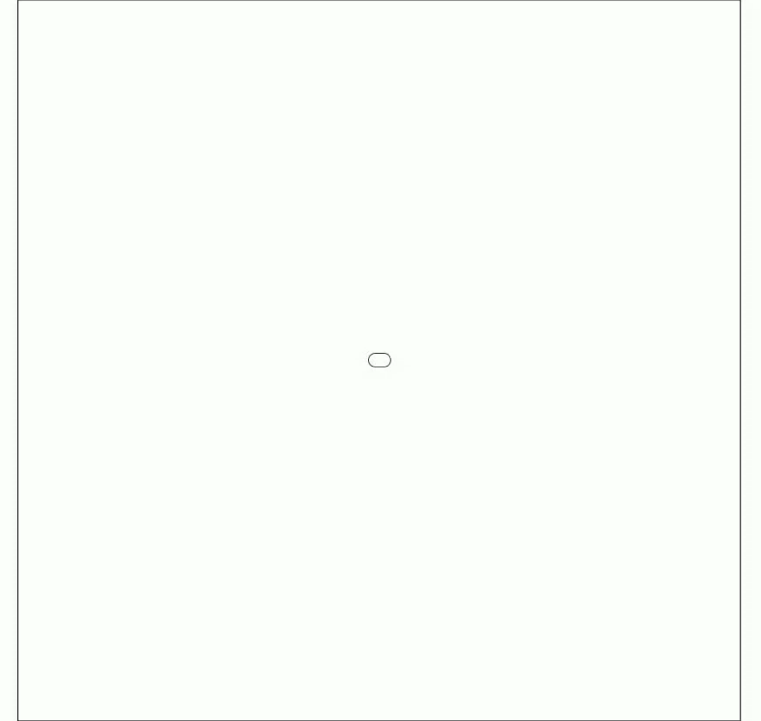
growth on glucose



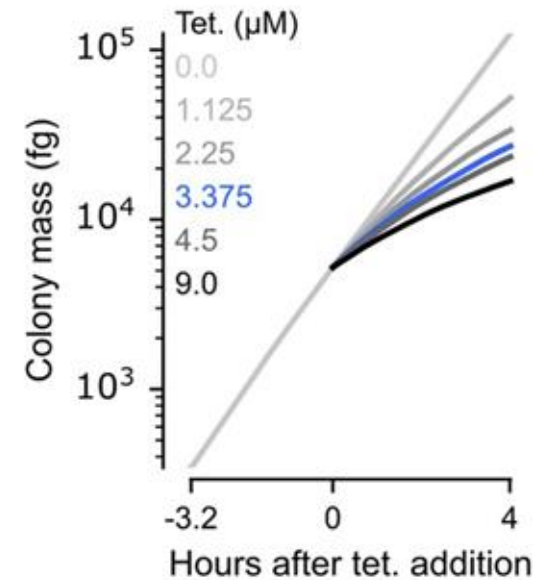
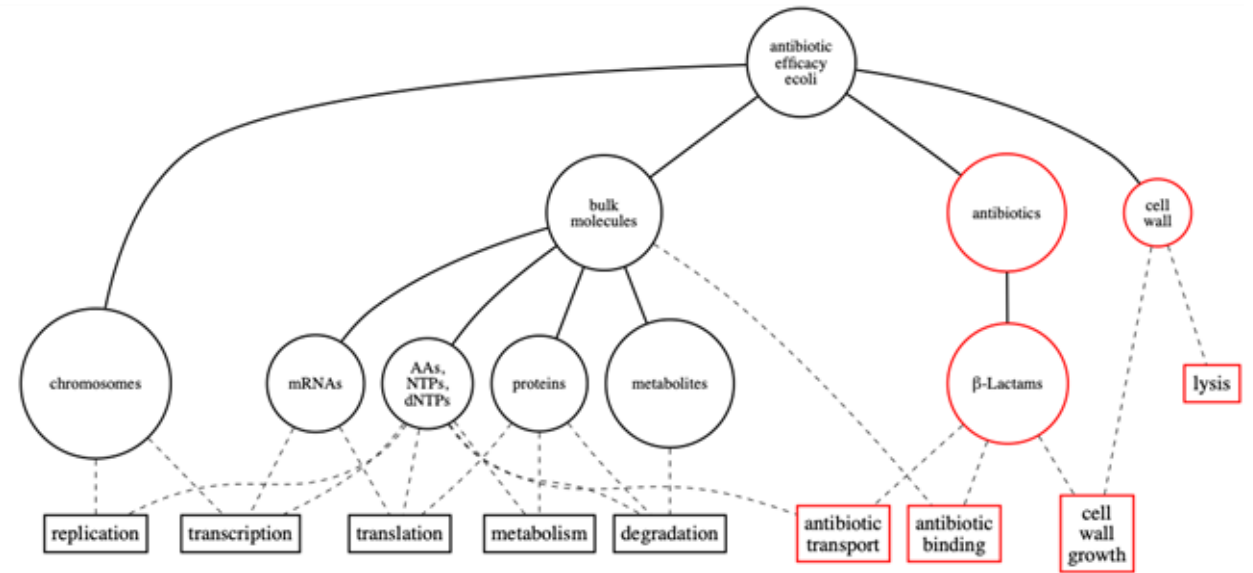
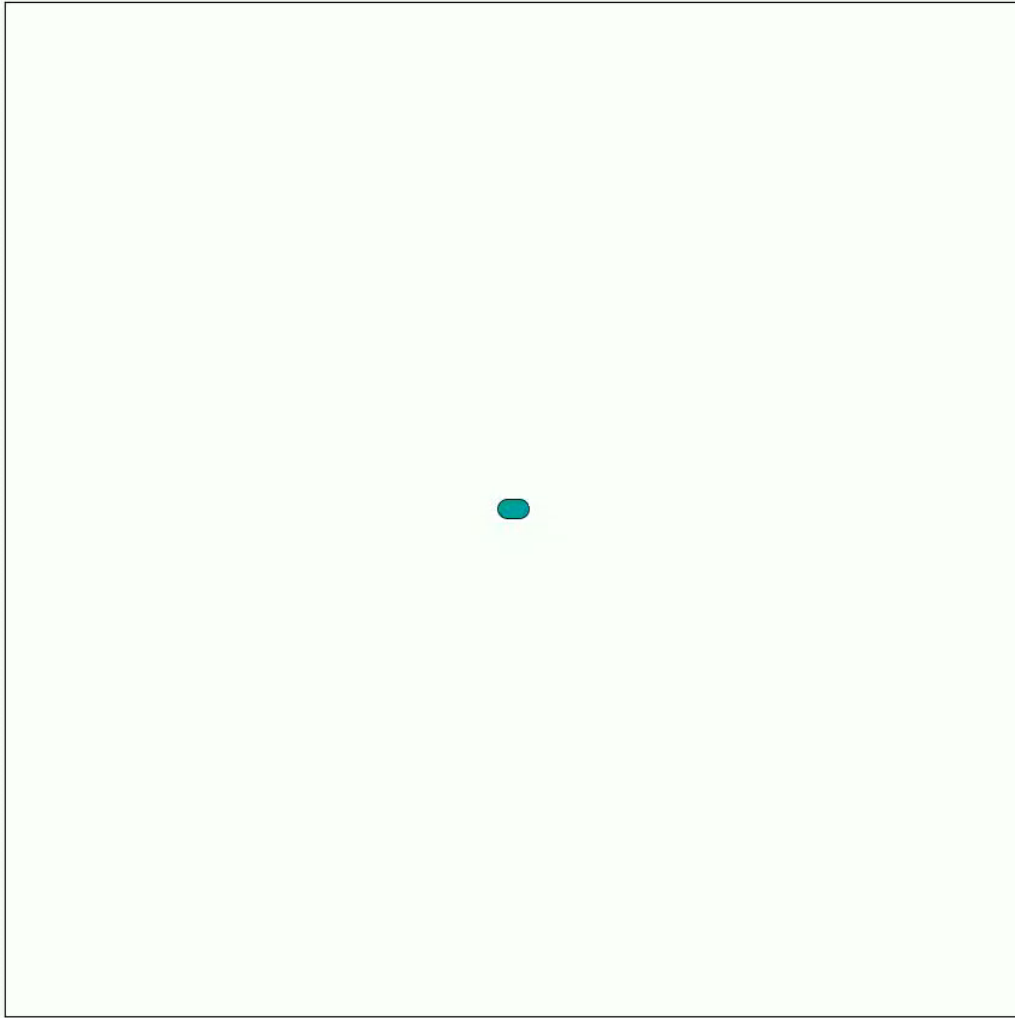
AmpC



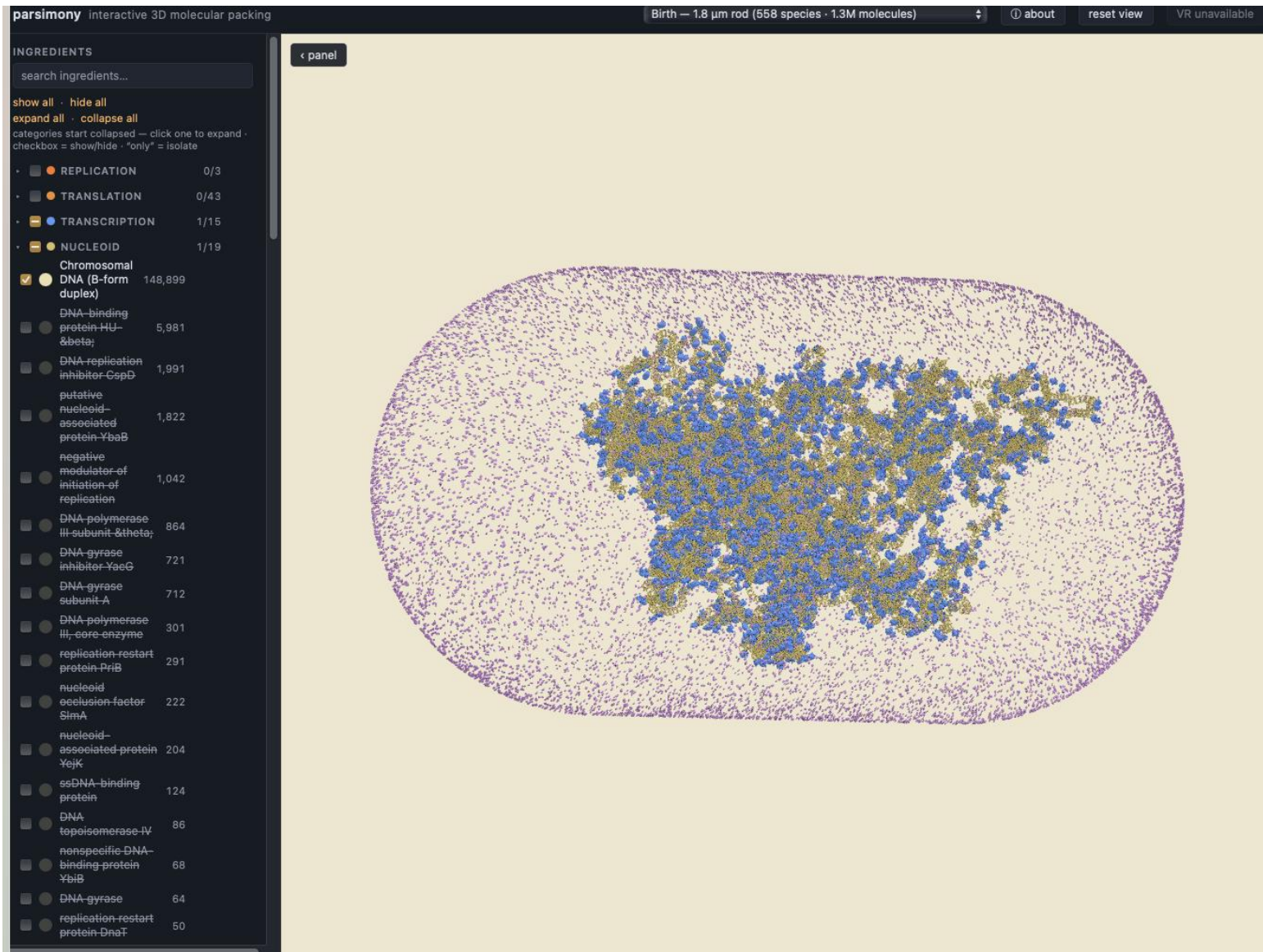
AcrAB-TolC



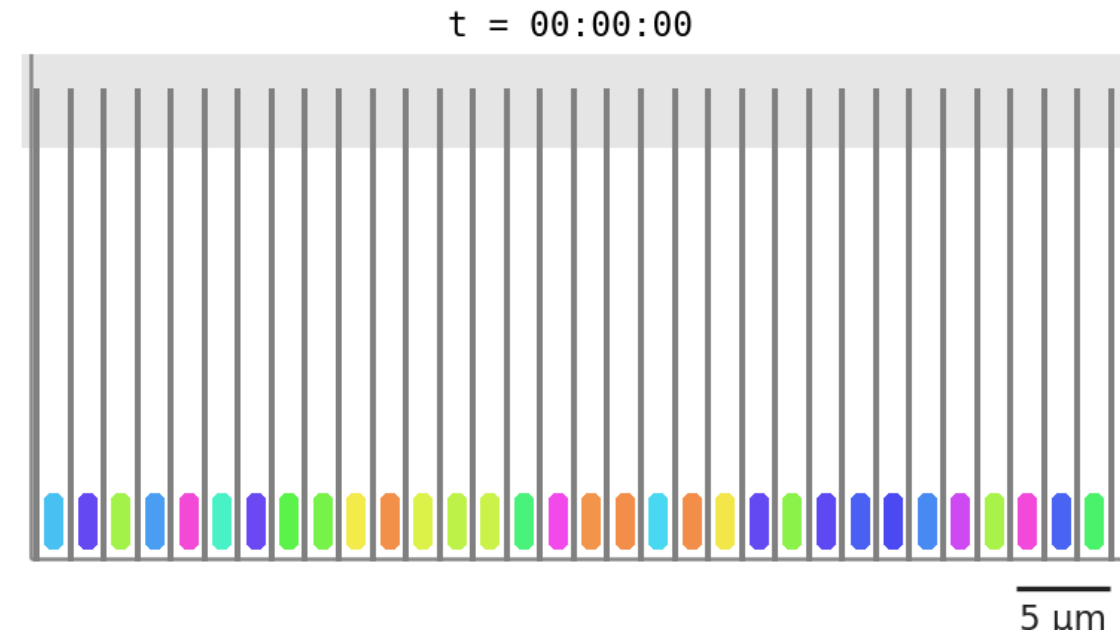
Adding function: response to antibiotics



Structural model of E. coli



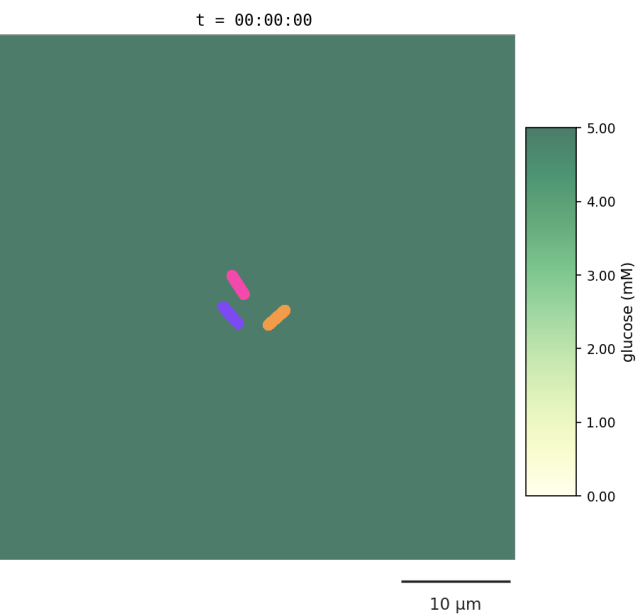
Mother Machine



Bending pressure + mechanoreception



Nutrient restriction



Chemotaxis





Simulating Microbial Systems (DARPA):

- Markus Covert (Stanford)
- Peter Karp (SRI International)
- Suckjoon Jun (UCSD)
- many more

Center for Reproducible Modeling (NIH):

- Herbert Sauro (Washington U)
- Ion Moraru (UConn Health)
- Jim Schaff (UConn Health)
- many more

Center for Chemical Currencies of a Microbial Planet (NSF):

- Mary Ann Moran (U Georgia)
- Heather Kim (Woods Hole Oceanographic Institute)
- Daniel Segre (Boston U)
- many more

And beyond:

- T.J. Sego (U Florida)
- John Hickey (Duke)
- James Glazier (IU)
- many more

Contact: agmon@uchc.edu

Website: <https://vivariumlab.com>

Vivarium Github: <https://github.com/vivarium-collective>



The Vivarium Lab is hiring several postdocs for newly funded projects. Please email for more information: agmon@uchc.edu