# A diversity-aware computational framework for systems biology

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PhD Program: Control and Computer Engineering

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POLITECNICO
DI TORINO

SYSBIO GROUP
SYSTEMS BIOLOGY AND BIOINFORMATICS

# Activities overview

*Scientific research and projects*

ScRNA-seq analysis

MITOR project for modeling diffusion

Pending patent for improving cell culture

HeartVdA national project

Diversity-aware computational framework for systems biology

2015

2019

I4C course

Training at TUM

Erickson school

Training and coaching for SEI

Tutoring Tech4Disability

*Soft skills and teaching activities*

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# Thesis statement

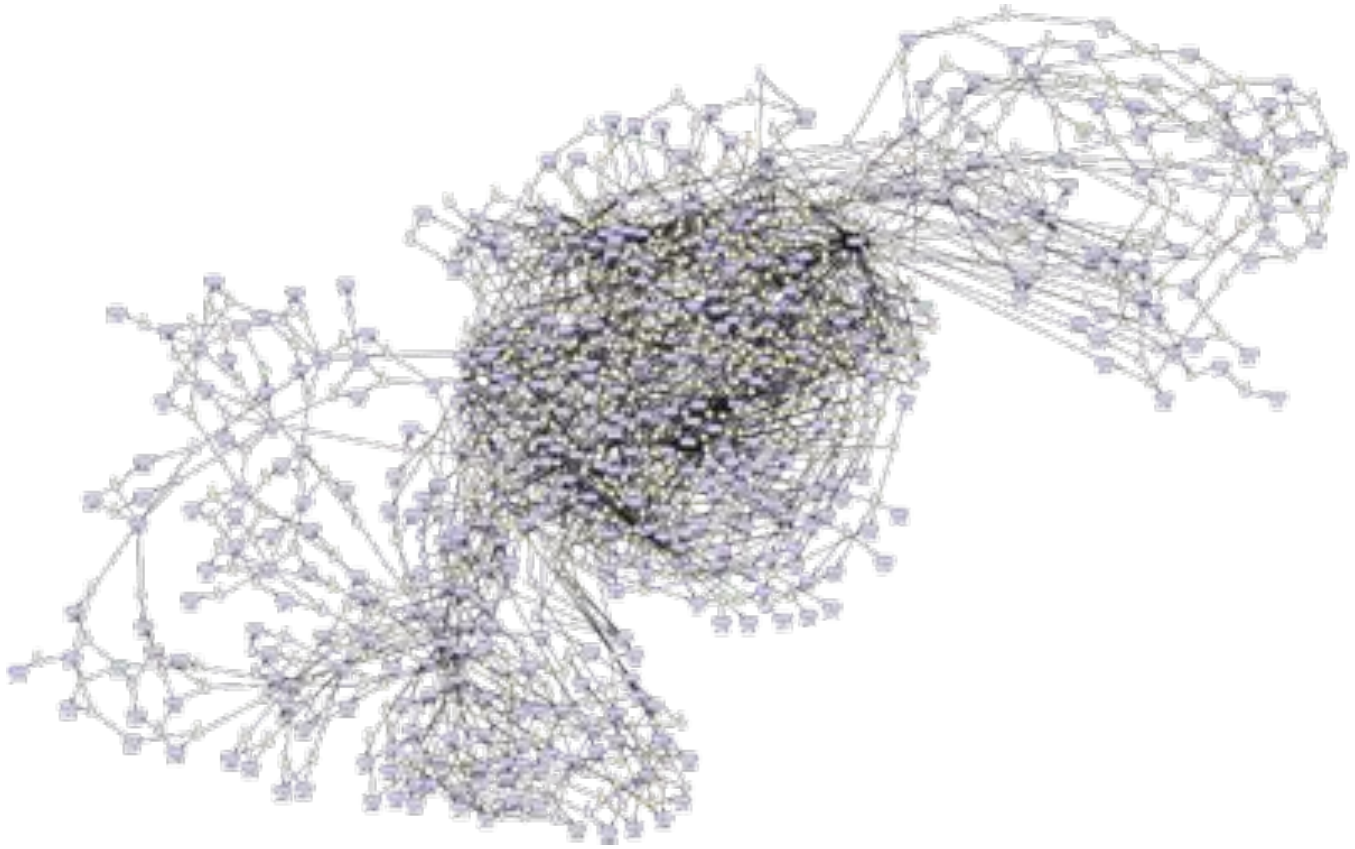
Different scientific domains contribute to systems biology.

A unified computational language for modeling biological systems could enable **interdisciplinary collaboration**.

The proposed **computational framework** includes a **modeling approach** for complex biological systems, and a model **description language** to make it usable for the diverse systems biology community.

# Outline

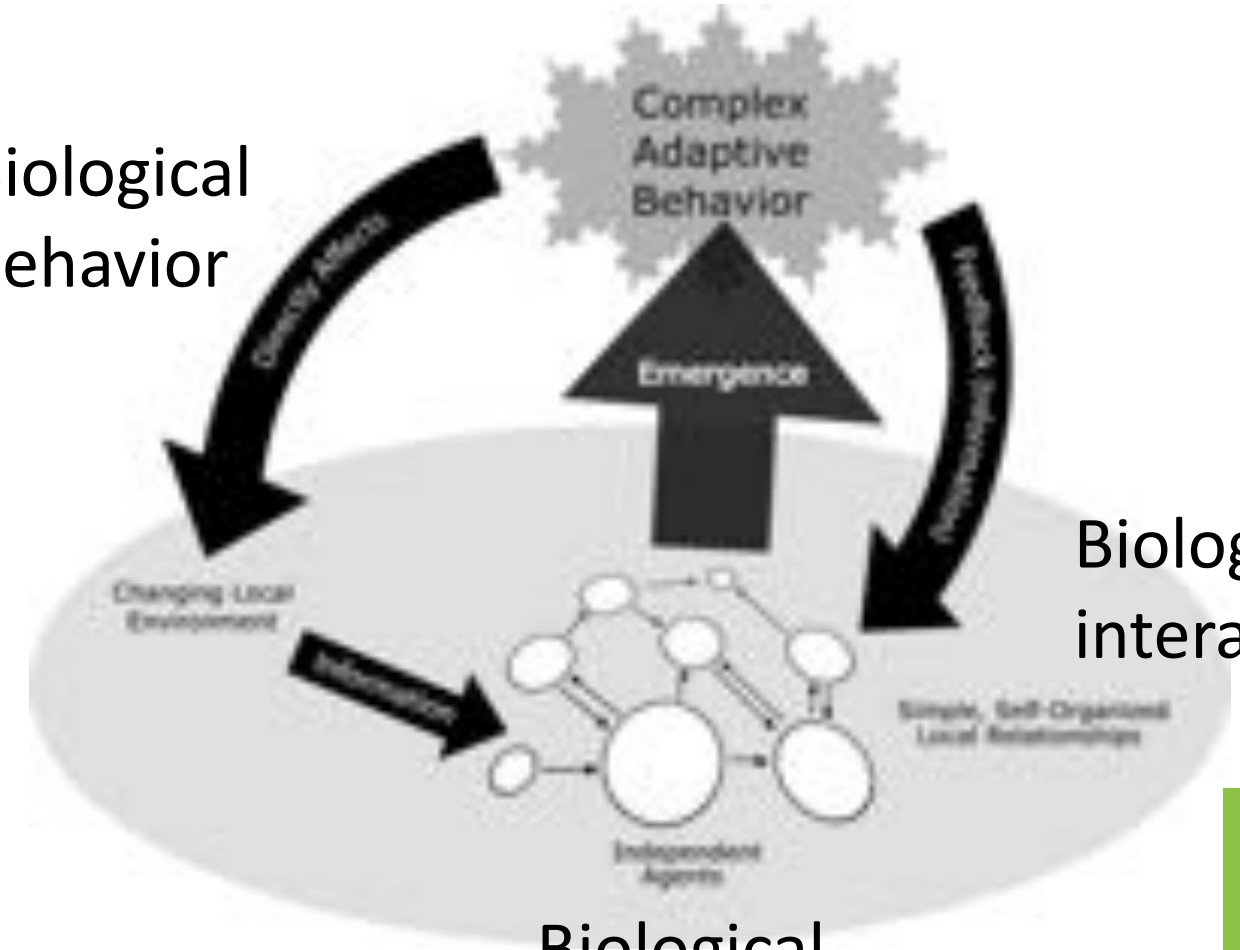
1. Biological complexity
2. Systems biology as a method
3. Systems biology as a domain
4. Managing knowledge
5. A diversity-aware computational framework for systems biology
6. Future perspectives



# 1. Biological complexity

# Biological systems are complex and adaptive

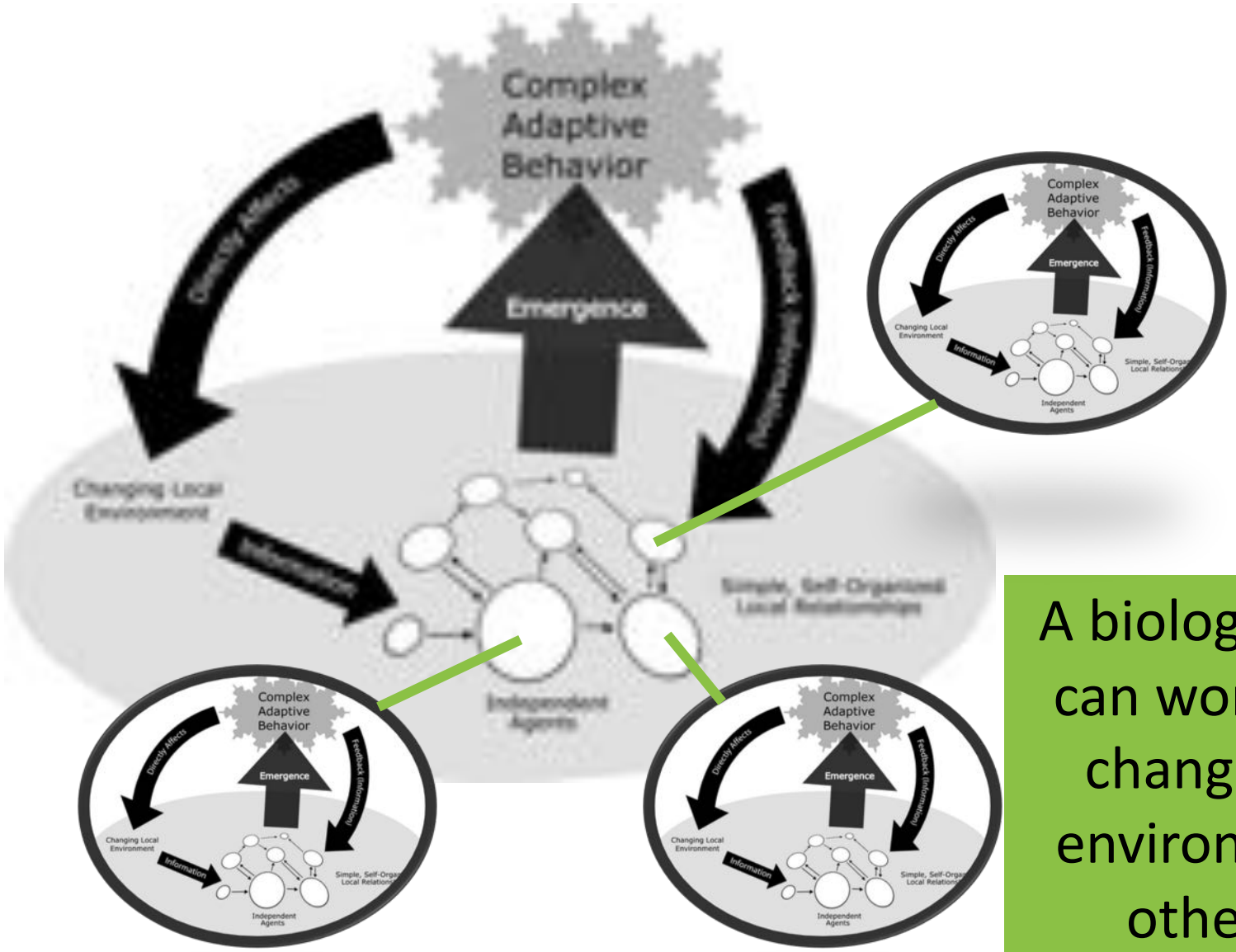
Biological behavior




Biological interactions

Biological entities

Complex biological patterns emerge from local interactions



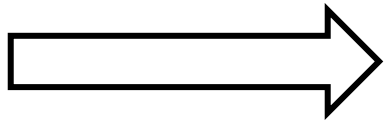

# Biological systems are multi-level

A biological entity can work as "the changing local environment" to other ones

# Biological local interactions

Potential interactions

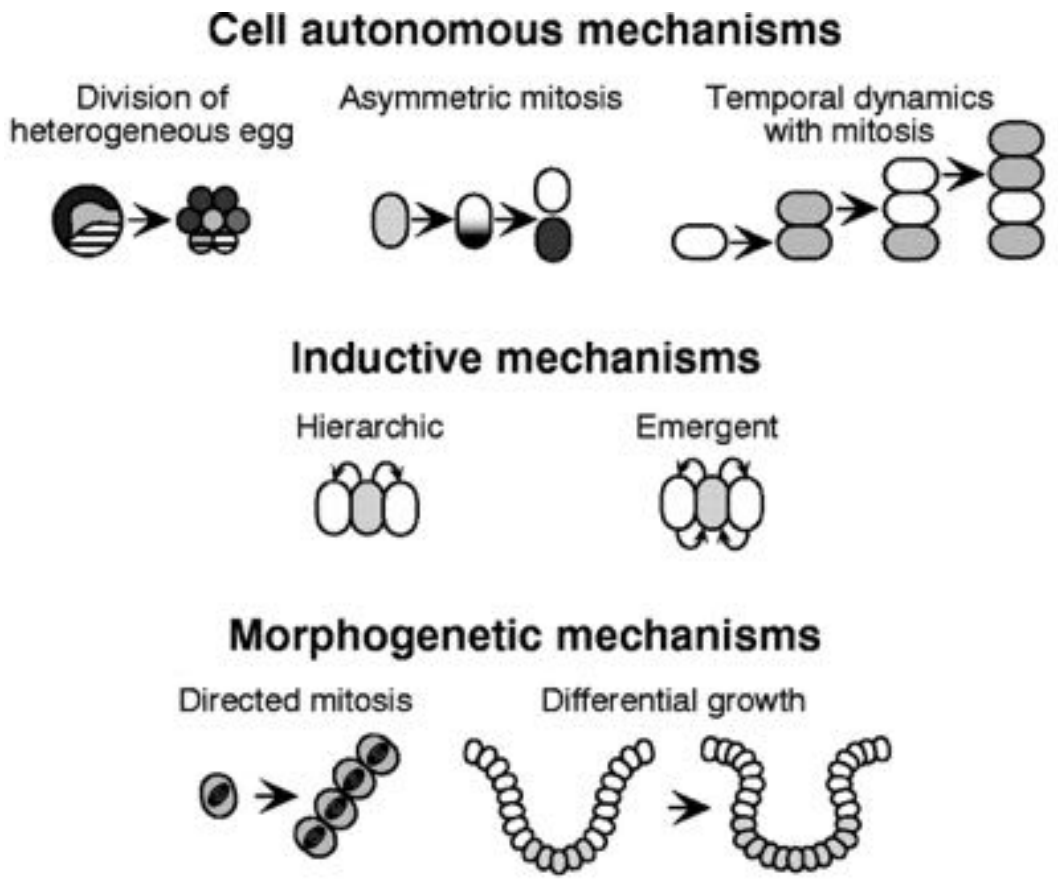
**Spatiality**



Actual interactions

Spatiality mediates functional interactions.

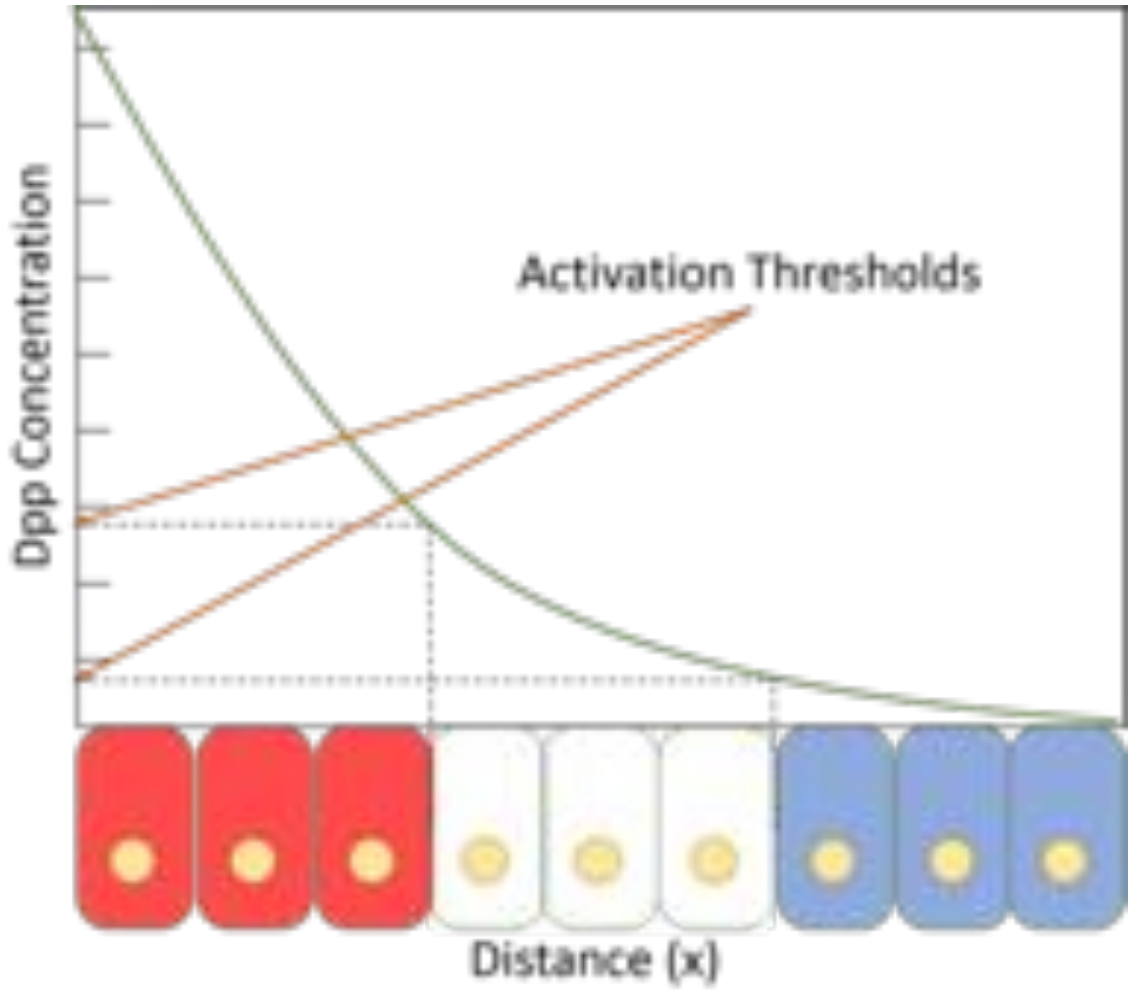

# Ontogenetic processes




# Basic developmental mechanisms

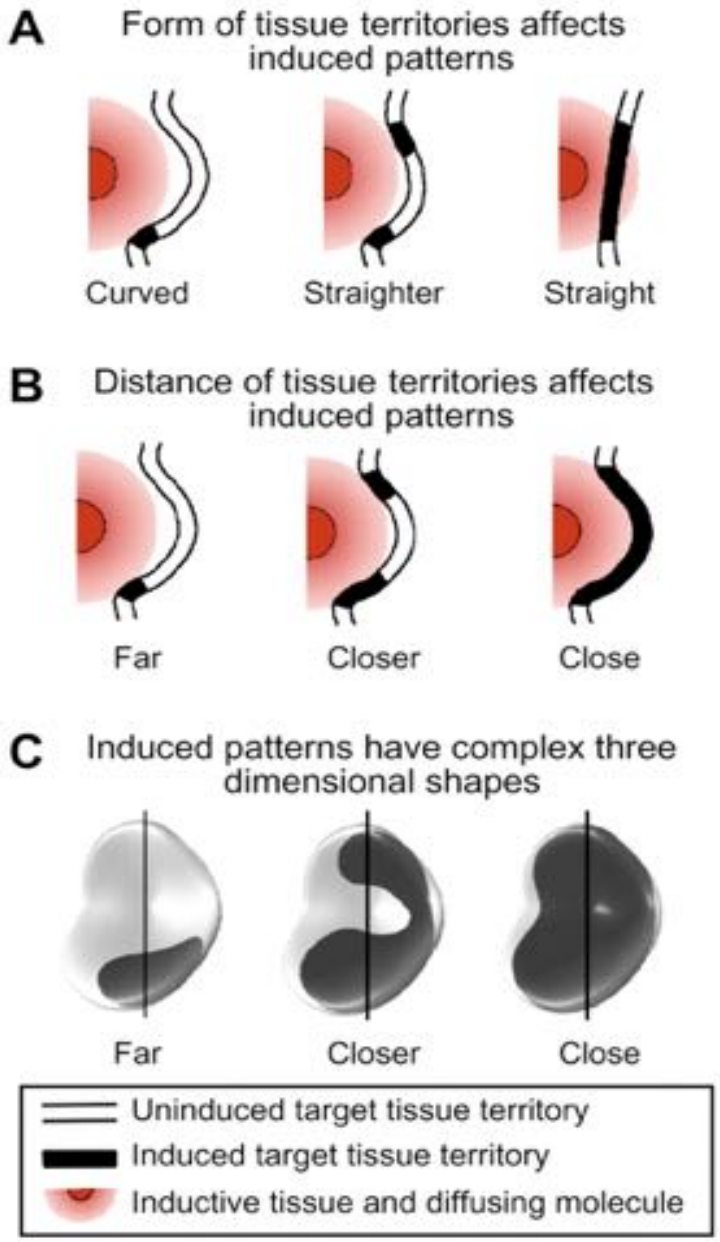
Local interactions occur at different system levels

*Adapted from Salazar et al, 2003*




# Morphogens gradients...

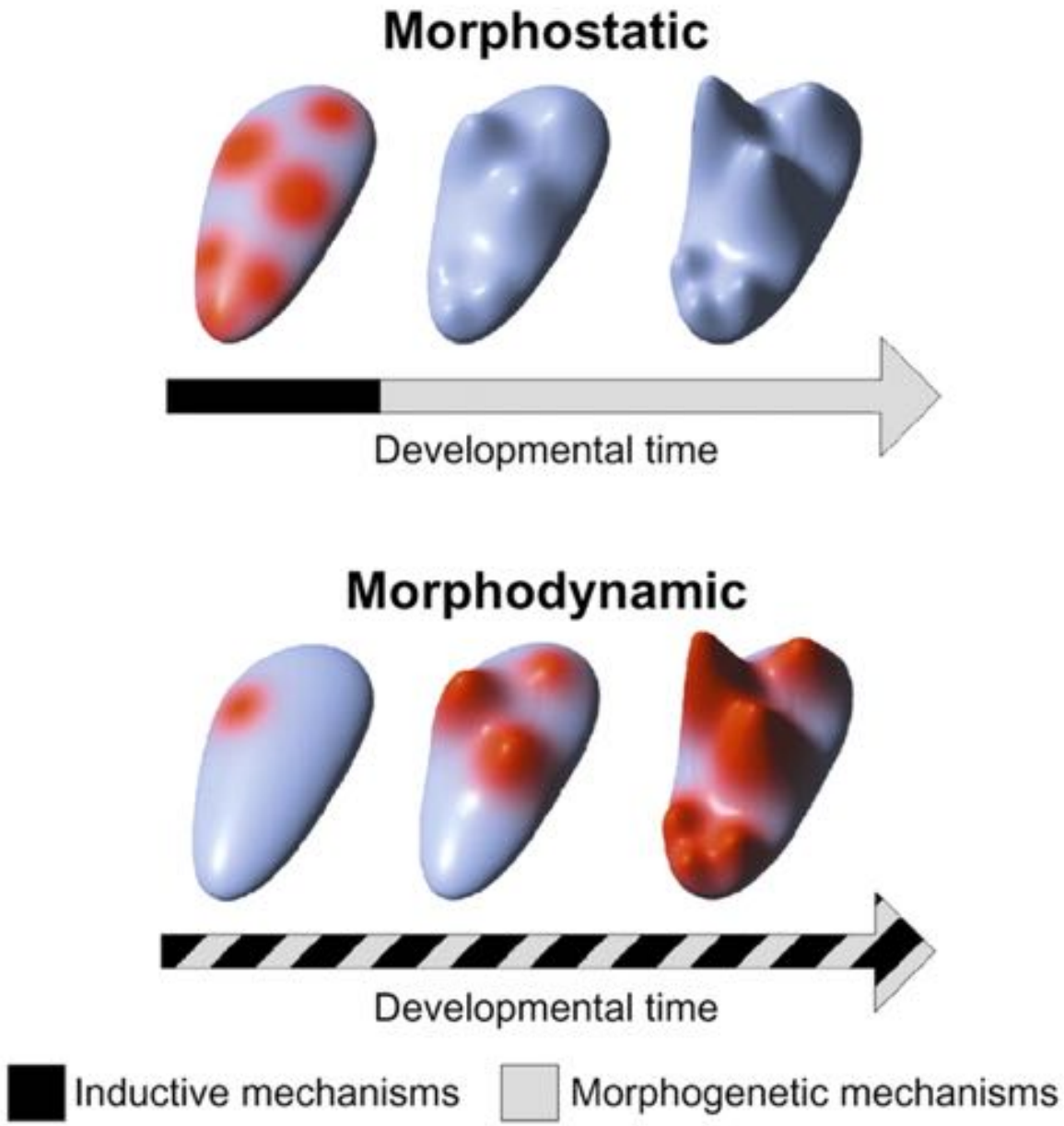
Morphogen gradients encode signals through distance




*Salazar et al, 2003*

# ...over complex shapes

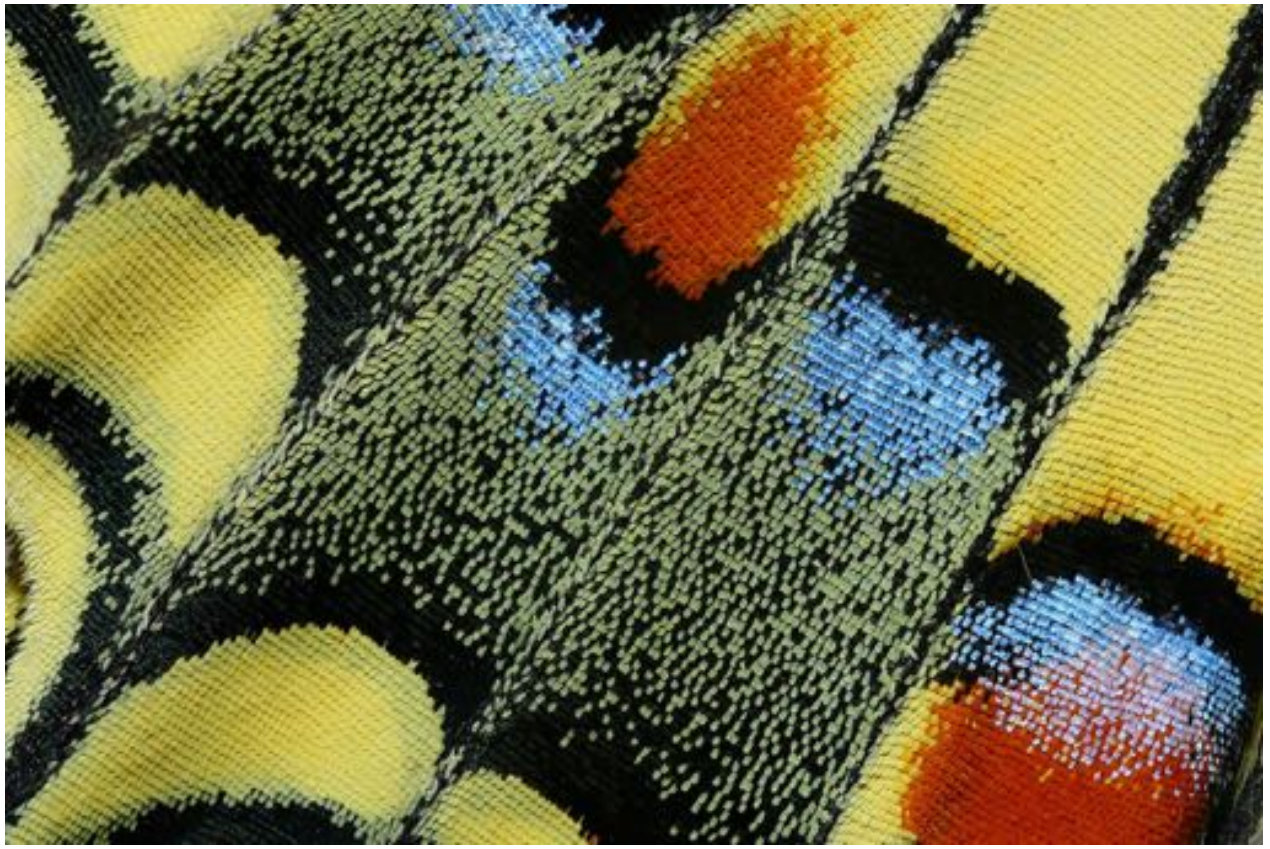
Multiple gradients in 3D space generate complex architectures



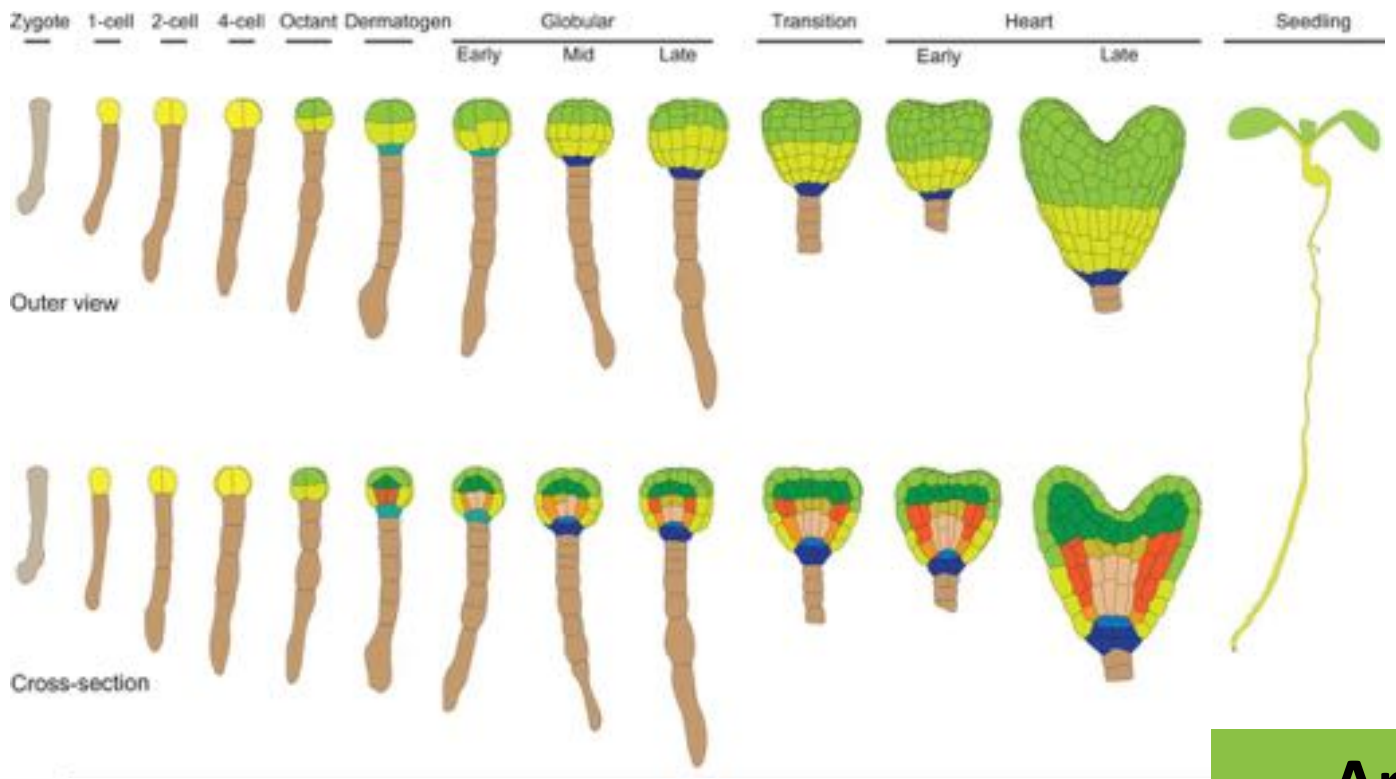

# Process organization

Local interactions at different levels take turns in temporal phases

*Salazar et al, 2003*



# Morphogenetic patterns

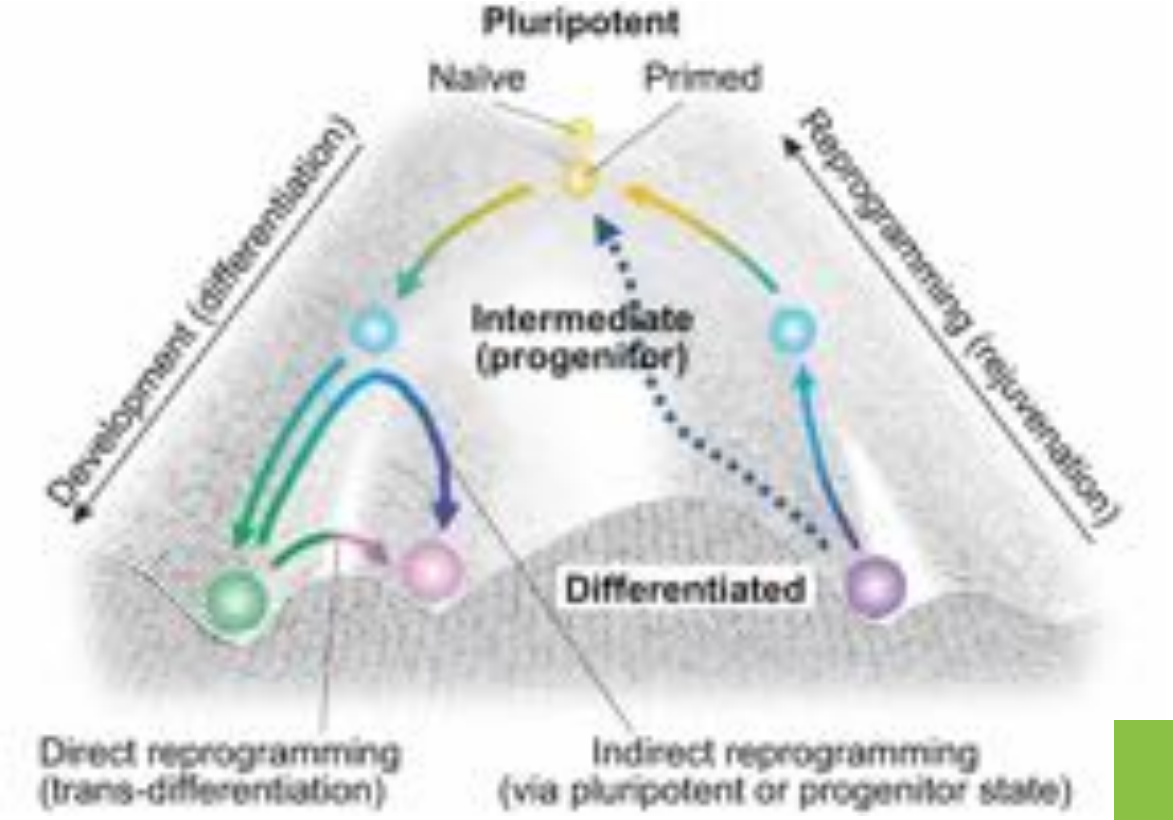



# A biological system taking shape

**Architectural** complexity emerges along development

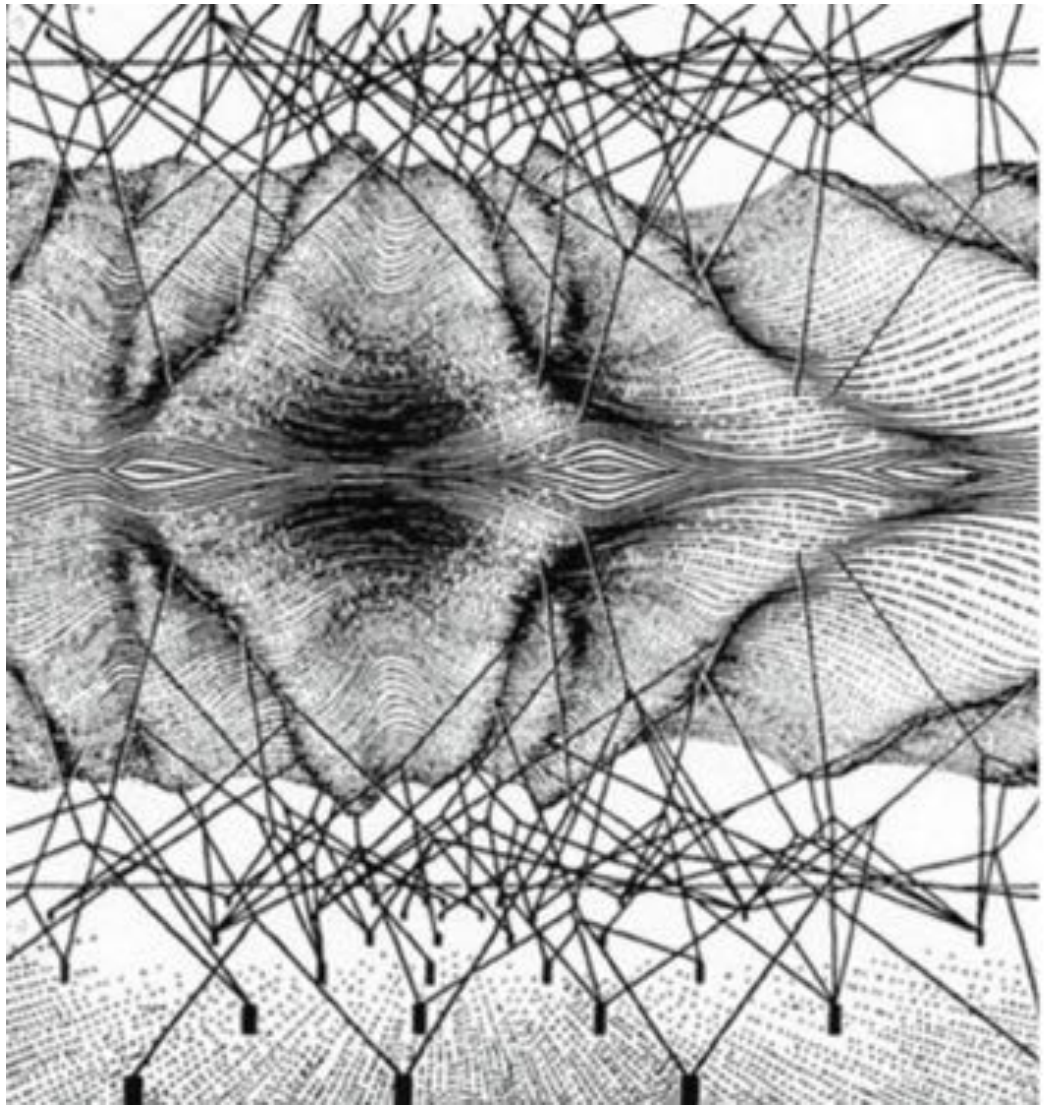
*Colette et al, 2015*

# Cell fates and differentiation




**Phenotype** complexity emerges along development

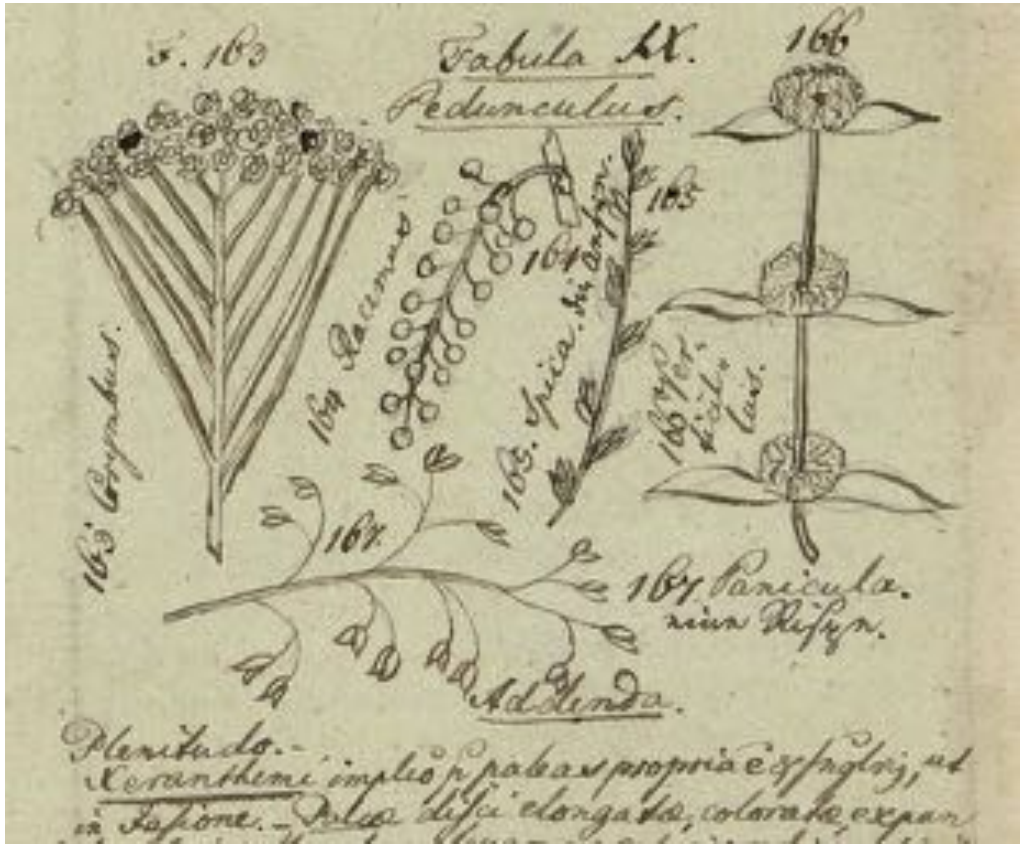
*Takahashi and Yamanaka, 2015*




# A dynamic landscape of regulations

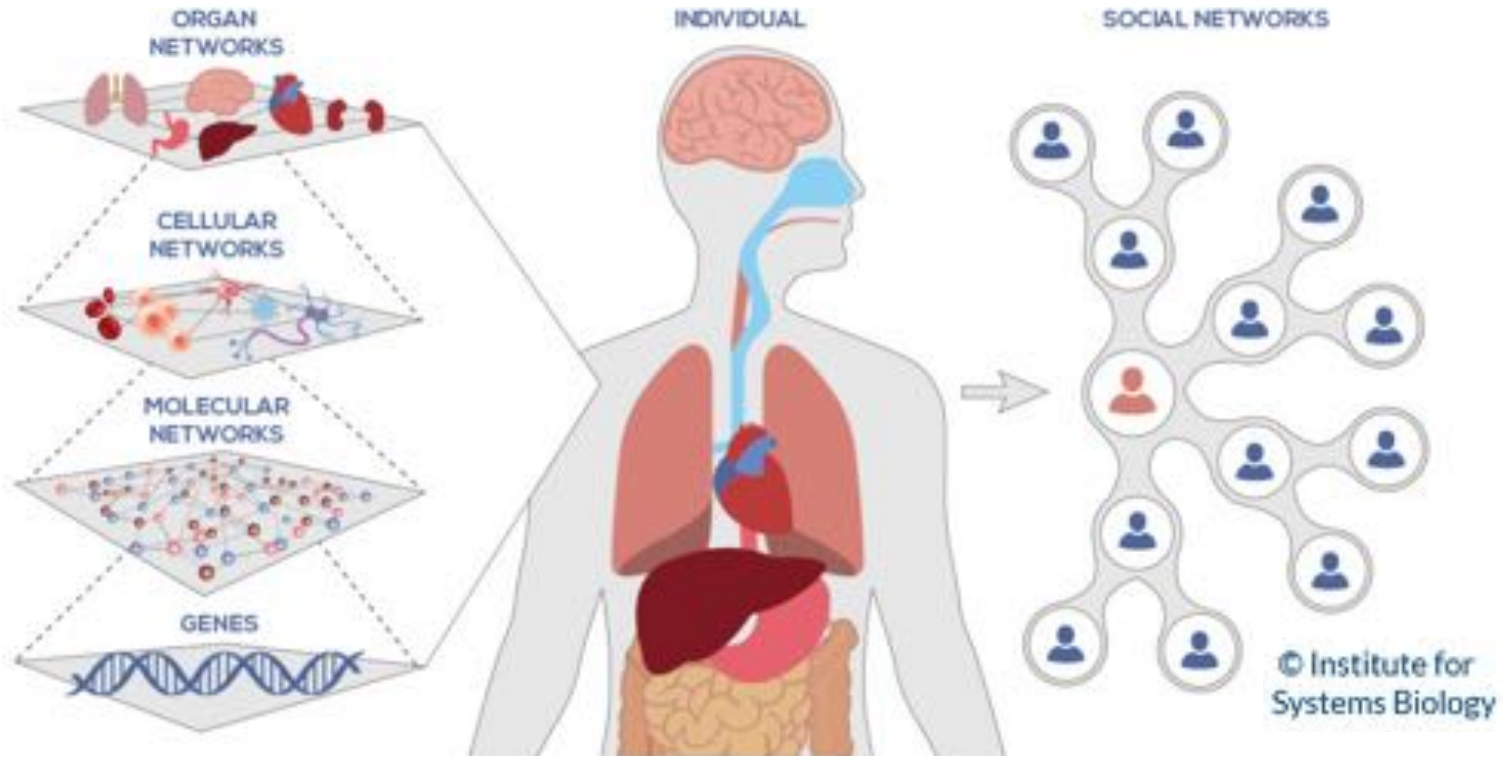
Genetic and epigenetic regulations draw a flexible hierarchy of regulations over morphogenesis.

*Noble, 2015 (modified from Waddington, 1957)*



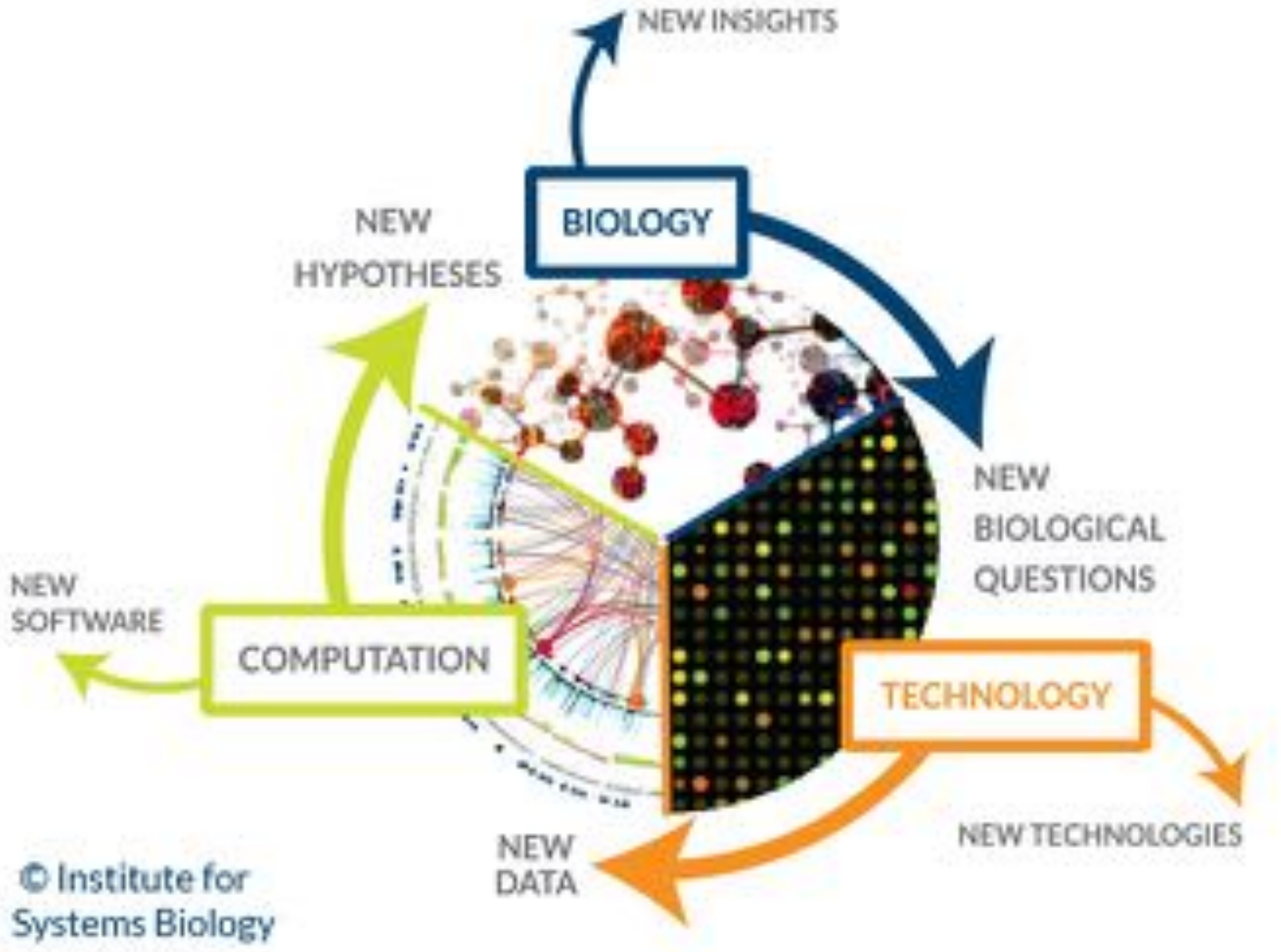

Botanical Notebook of Linnaeus, ca 1751, World Digital Library

# 2. Systems biology as a method



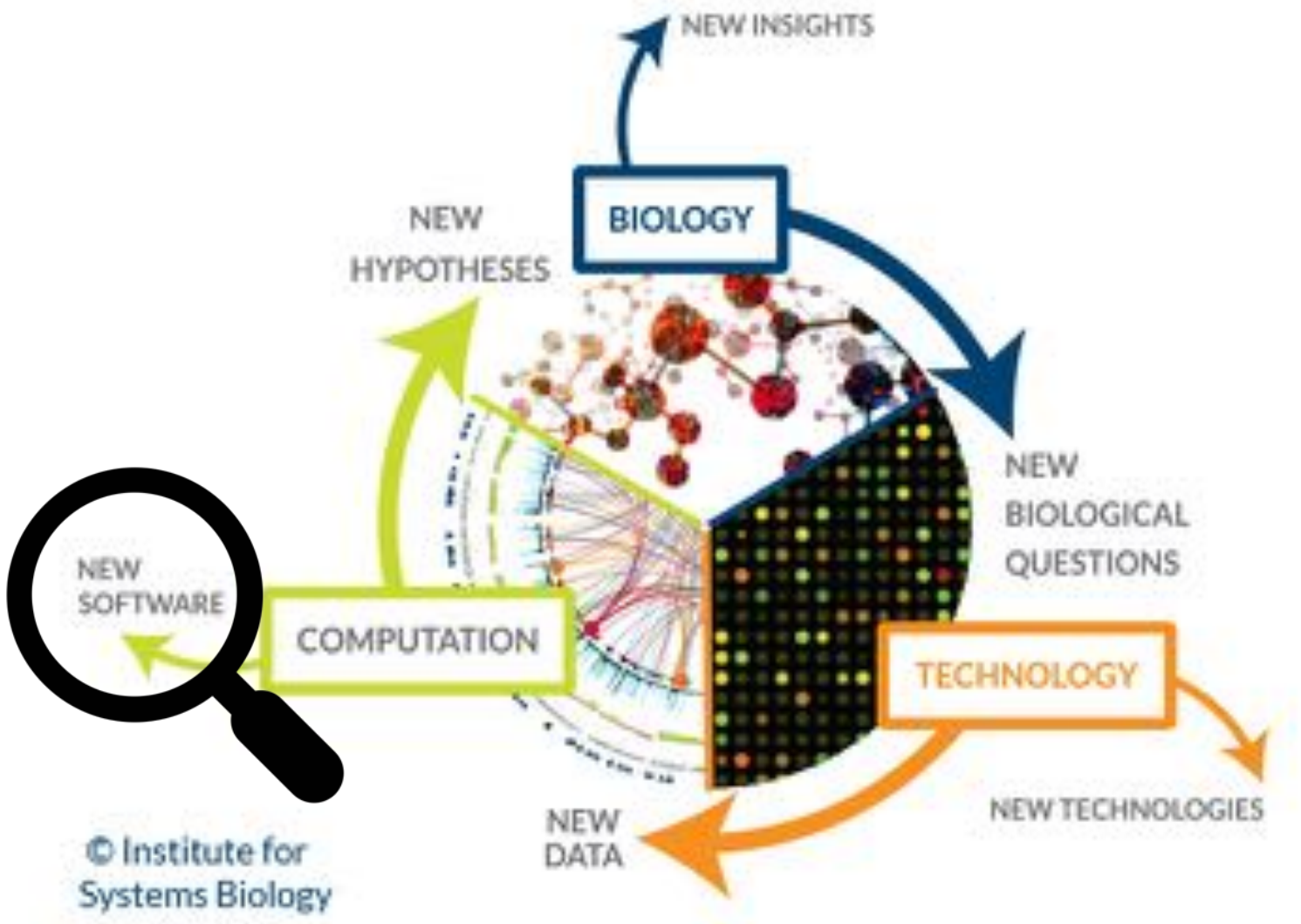

# Multiple organization levels

Systems biology organizes reductionistic explanations in schemes of relationships...



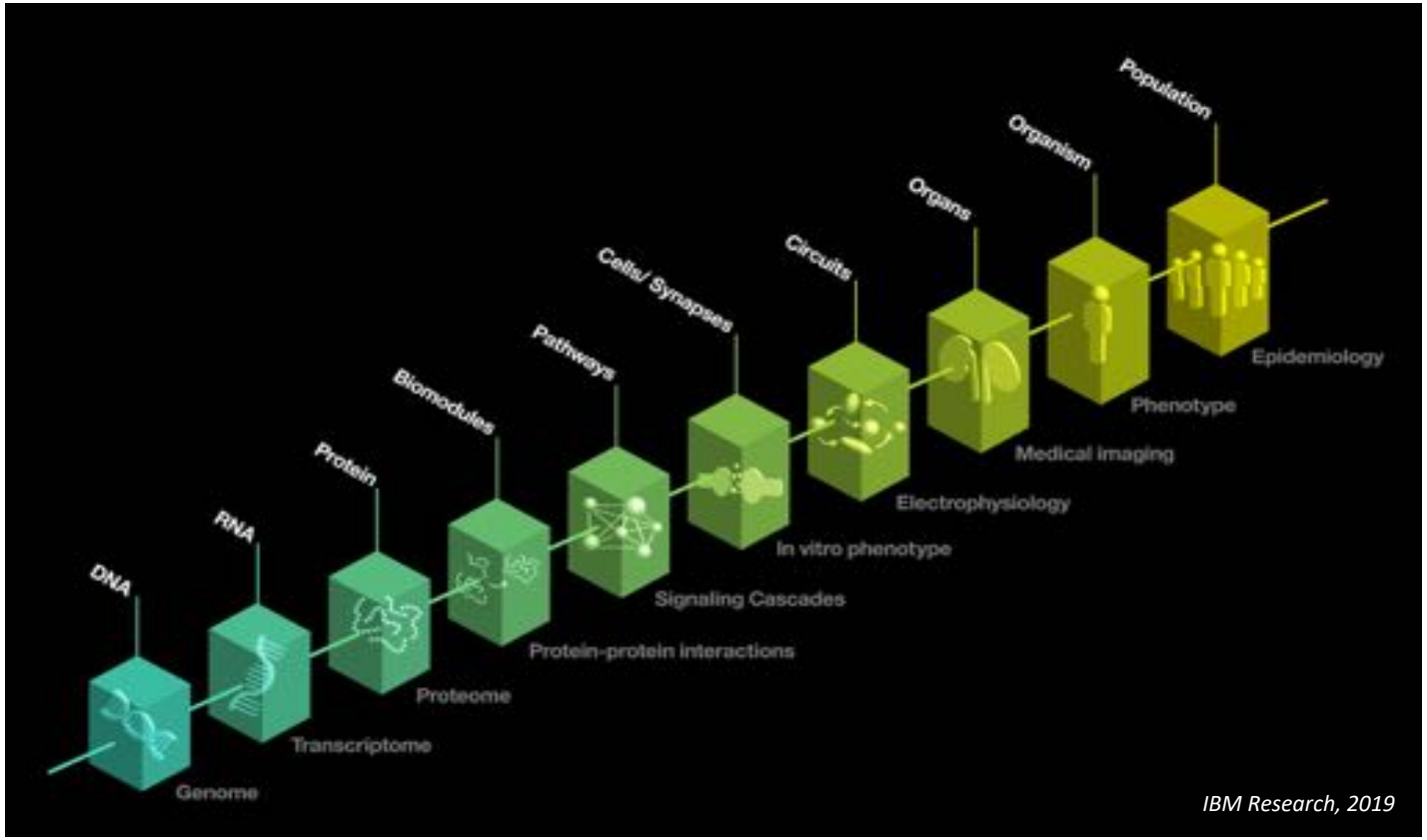

# The systems biology circular pipeline

...embedding quantitative data into functional representations to generate new hypothese to test in the lab.

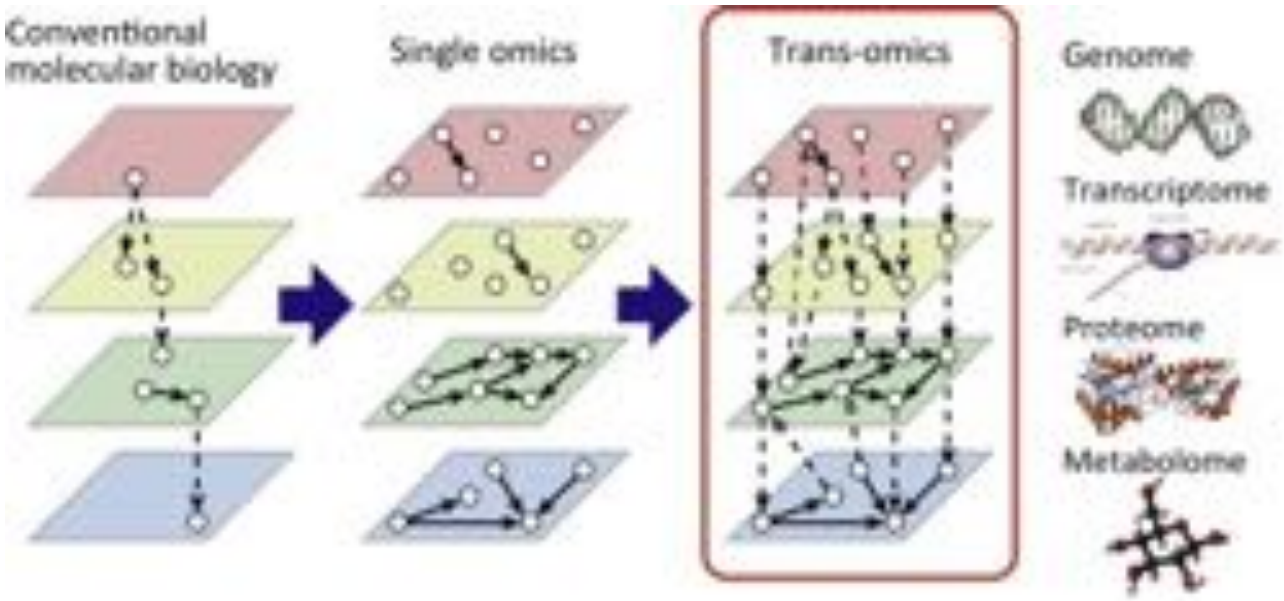



# The systems biology circular pipeline

This work focuses on computational approaches for systems biology.



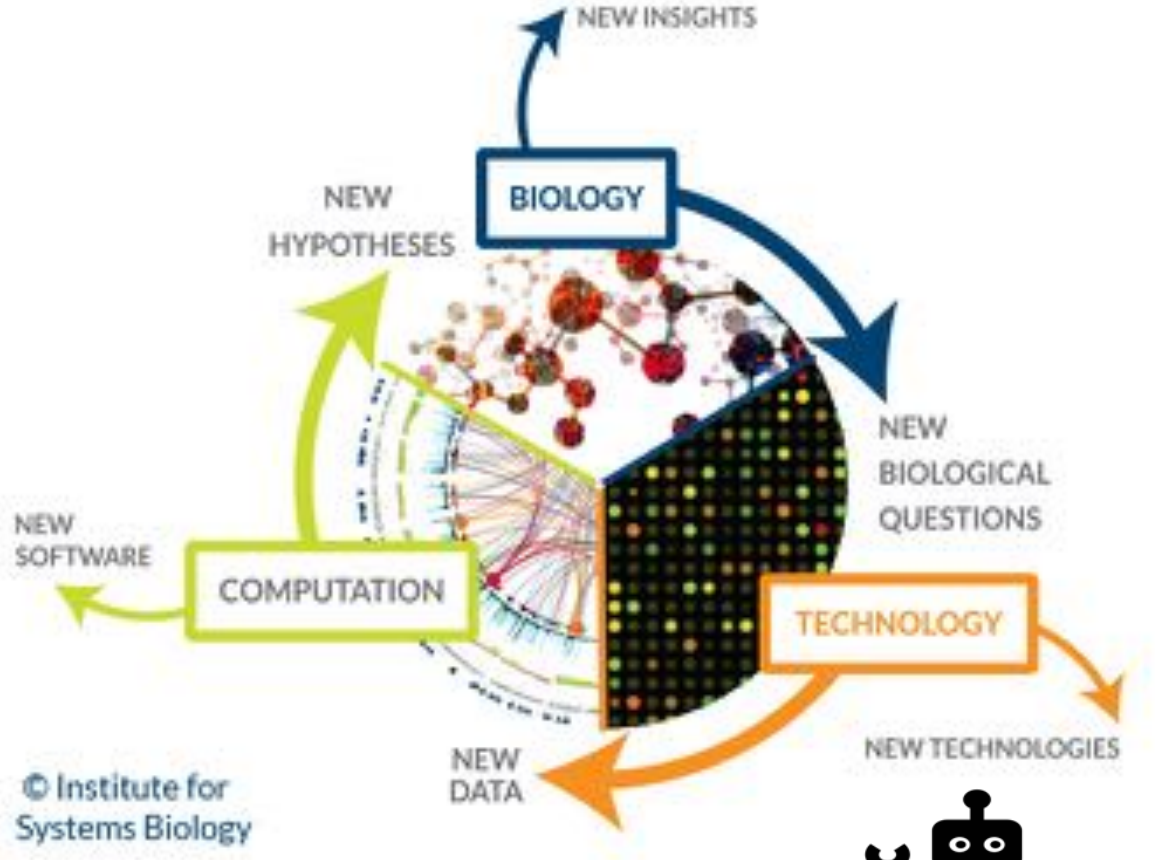

# 3. Systems biology as a domain

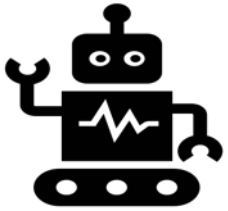



Yugi et al, 2016

# Different types of information

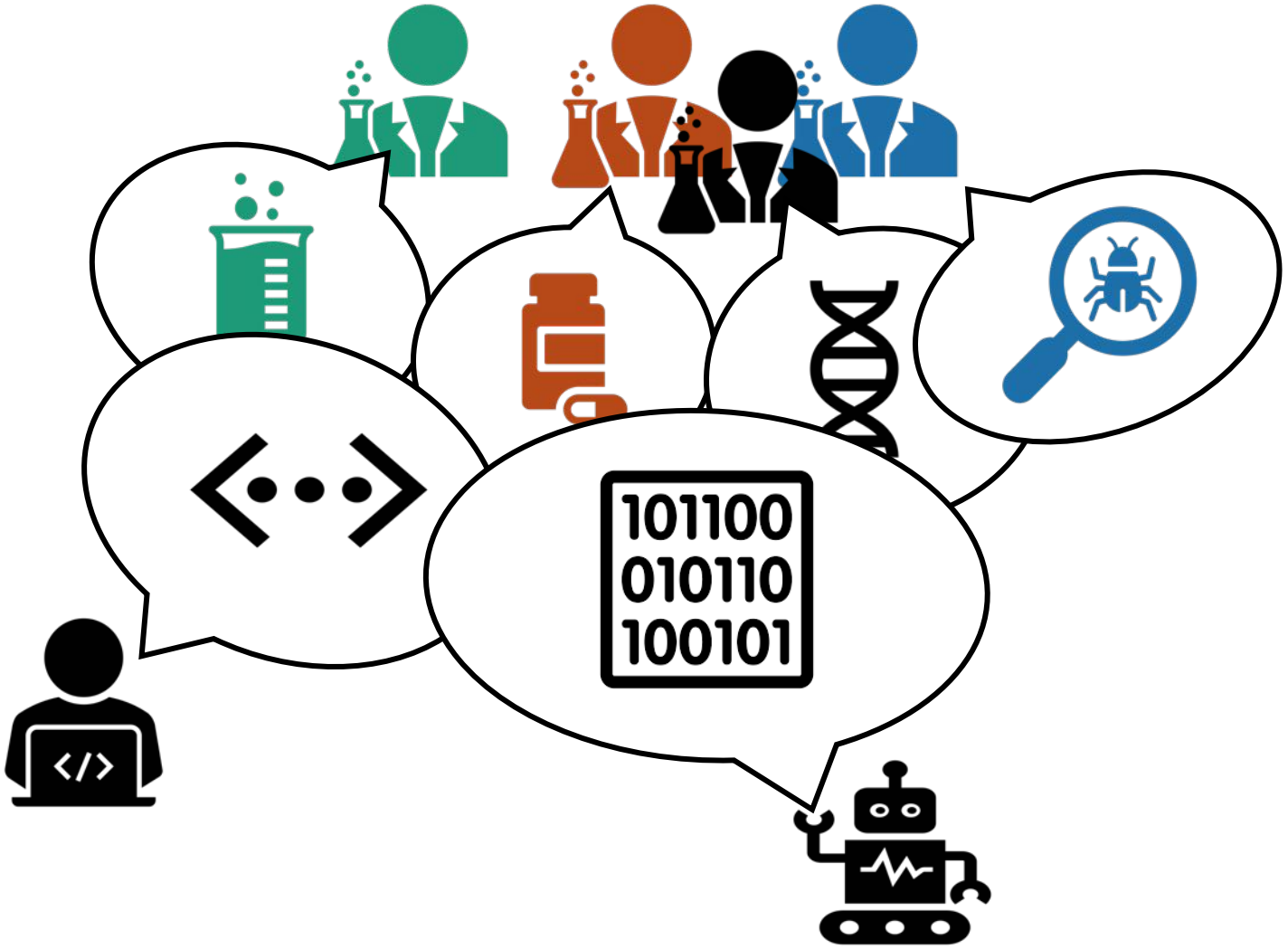
Considering multiple system levels implies comprising information from **different biological branches** and ***omics***...



# Different scientific cultures

...cultures (even within the same group of experts)...

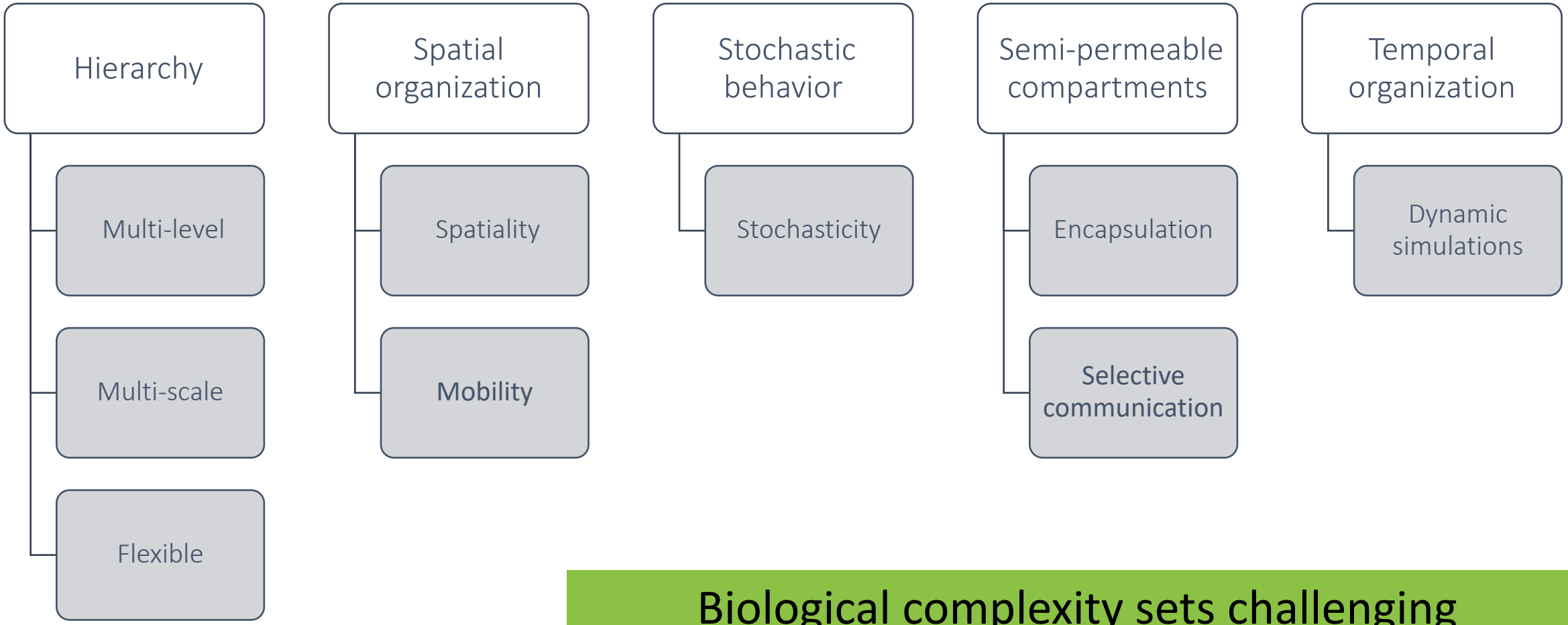



# Different ways to express knowledge

...and languages.

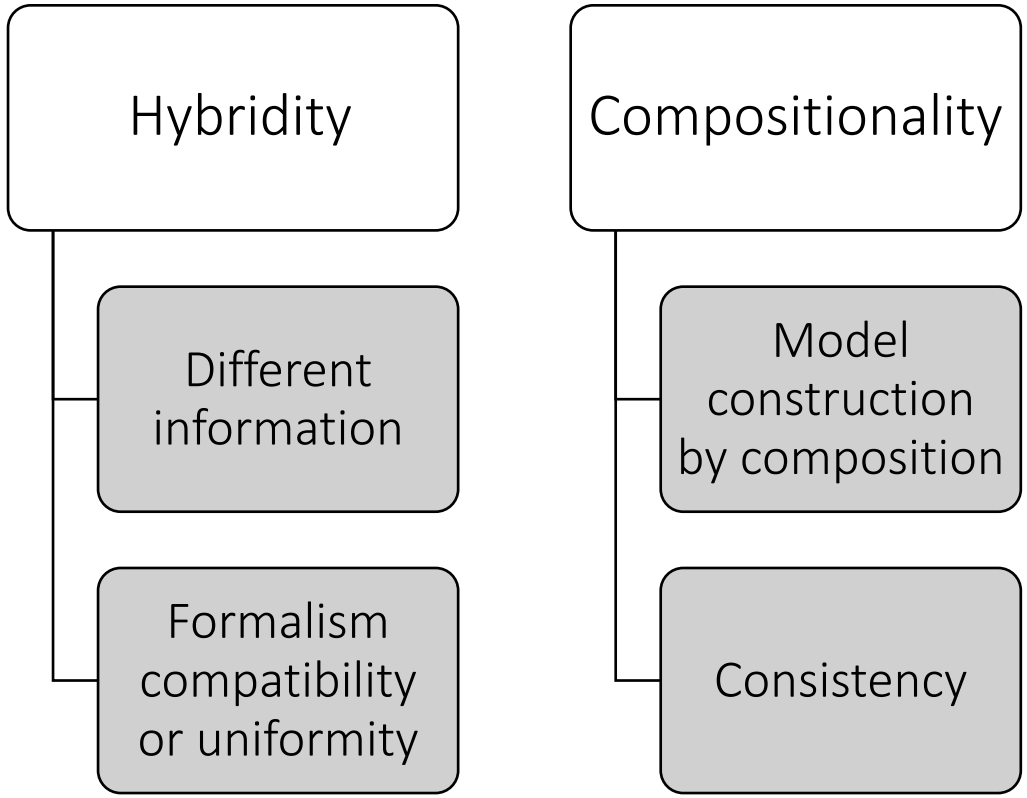
# 4. Managing knowledge

# Models to **represent** and **infer** knowledge



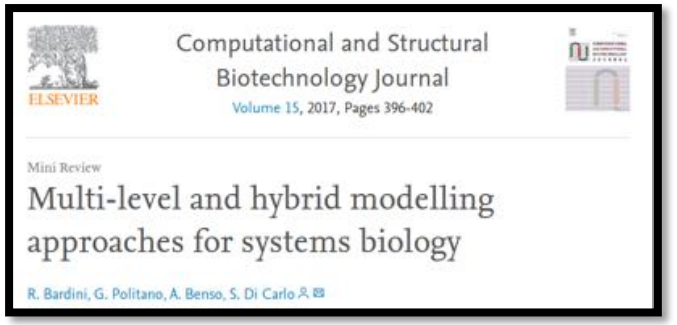

Biological complexity sets challenging requirements for computational models

# Models for knowledge **integration**




Leveraging available knowledge and information requires to adapt to its current form.

# Models for knowledge **integration**




- Hybridity
  - Different information
  - Formalism compatibility or uniformity
- Compositionality
  - Model construction by composition
  - Consistency

Multi-level and hybrid models for systems biology tend combine different formalisms with problem-specific strategies.

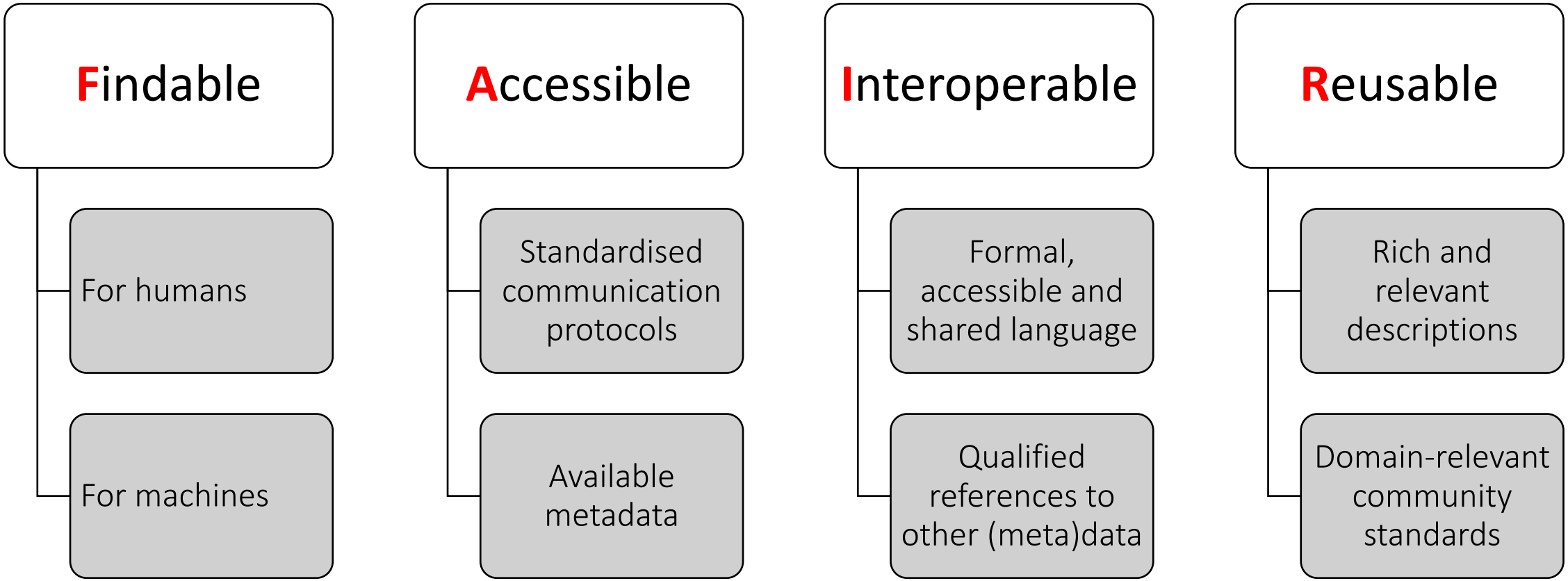
# Towards real **interdisciplinarity**

"Integrating knowledge and methods from different disciplines, using a real **synthesis** of approaches, towards the creation of a **unity** of intellectual frameworks **beyond** the disciplinary perspectives"

Interdisciplinarity requires generality and formalism uniformity.

*Jensenius, 2012*

# Models to **represent** and **exchange** knowledge

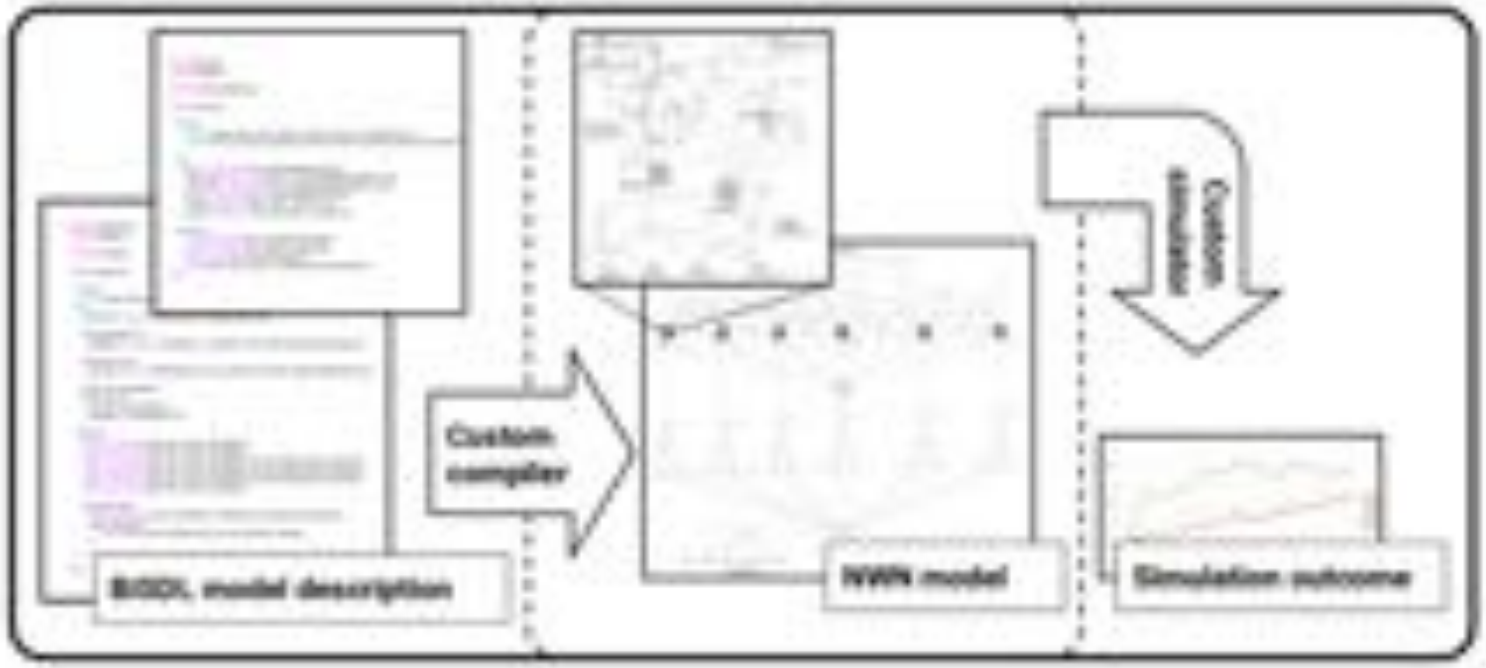



Representations of biological systems need to be **F.A.I.R.**

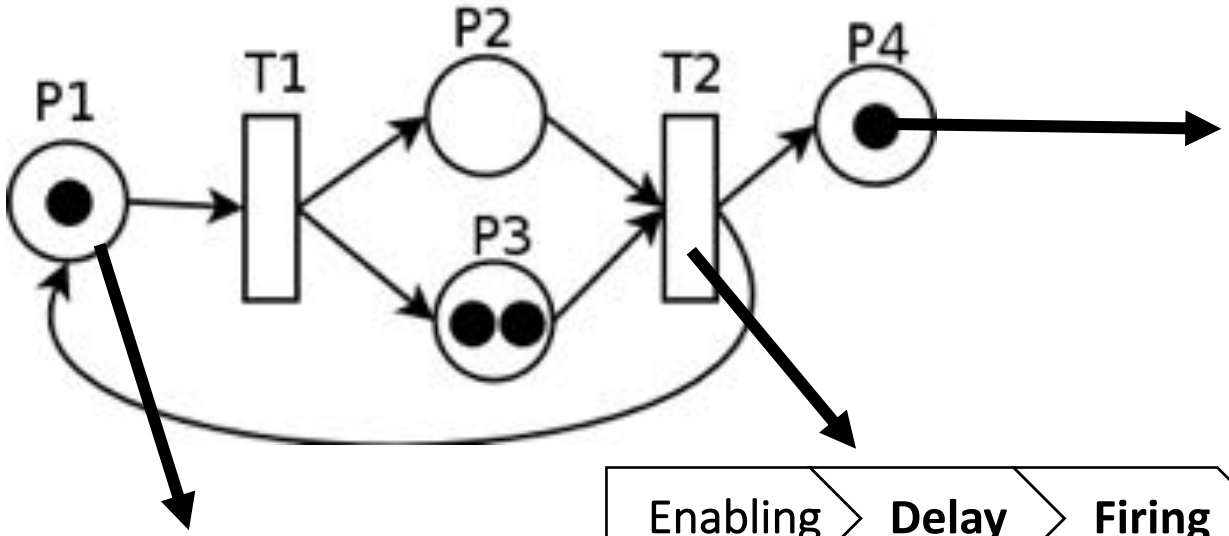
*Wilkinson, 2016*

# 5. A diversity-aware computational framework for systems biology

# The Framework




The Framework includes a **modeling approach** and a **description language** to make models accessible to the entire systems biology community.




Discrete quantities of **resources**

**States** of resources (*Protein A, protein B, gene X, ...*)

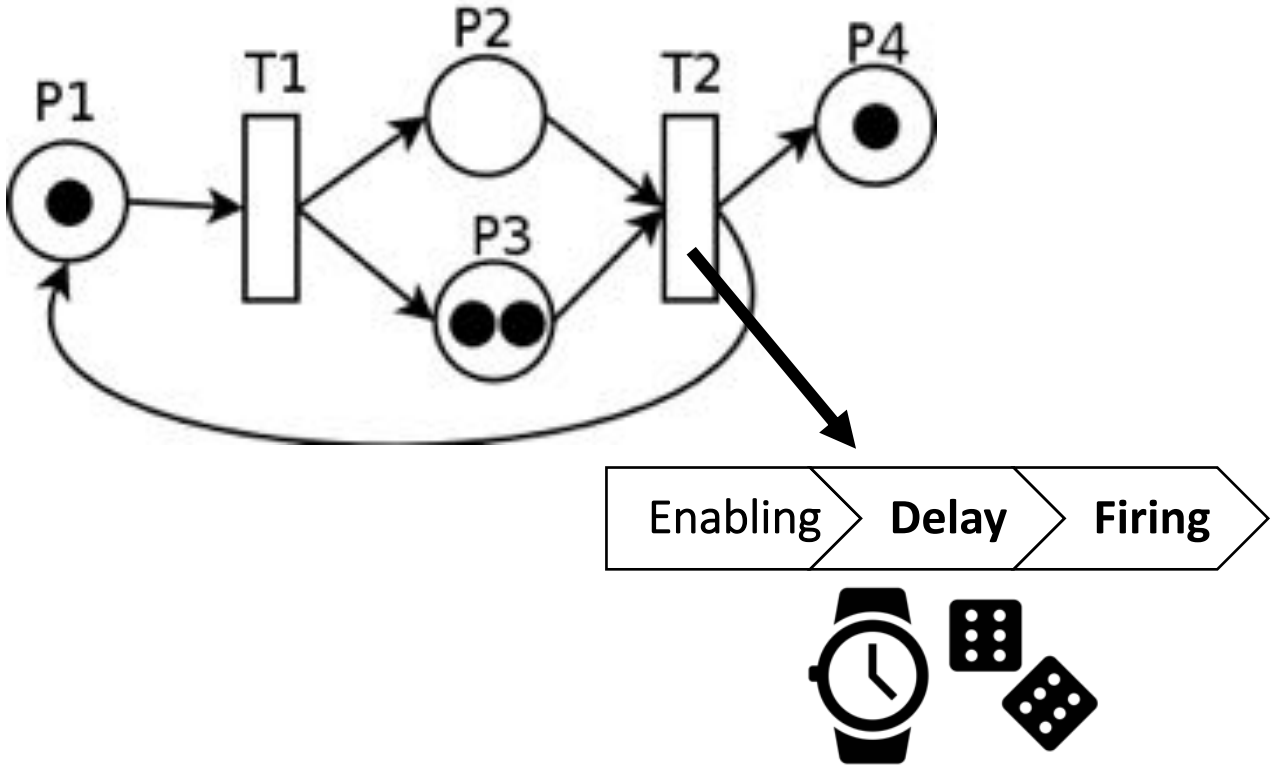
Enabling **Delay** **Firing**

**Transformation** of resources (Transcription, protein activation...)

# Petri Nets

Petri Nets are visual, mathematically defined and executable.

# Petri Nets



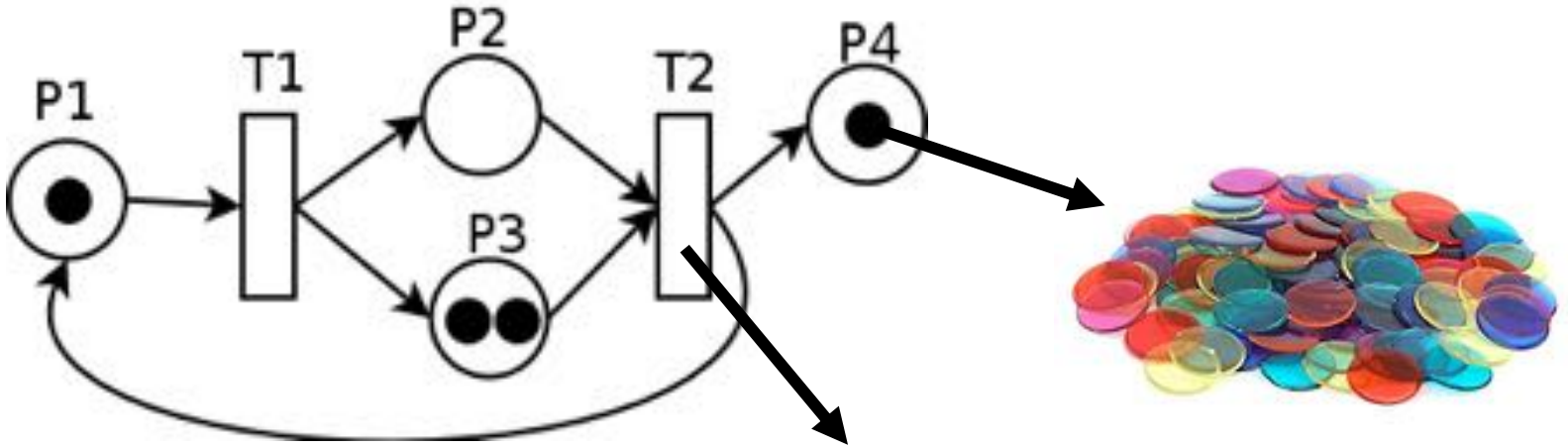

Petri Nets are visual, mathematically defined and executable. Expressing timing and stochasticity.

Tokens: discrete quantities of resources.

Places: states of resources.

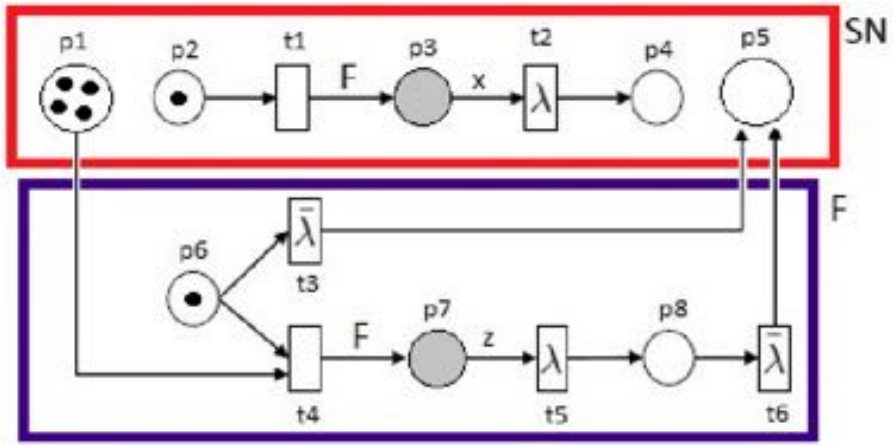
Transitions: transformation of resources.

# Petri Nets






Enabling | **Delay** | **Firing**

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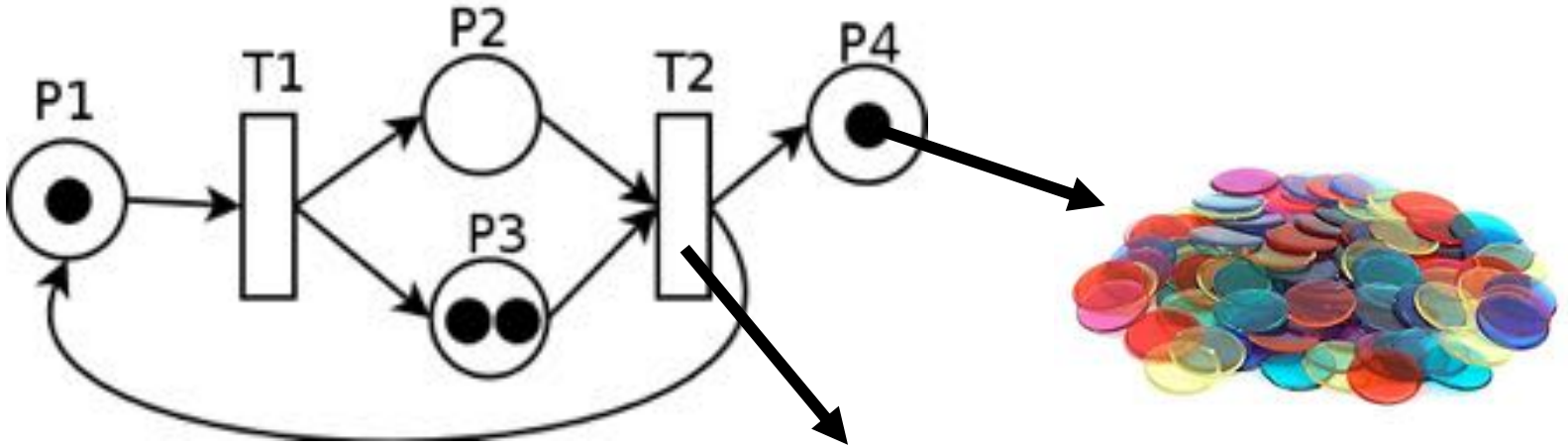
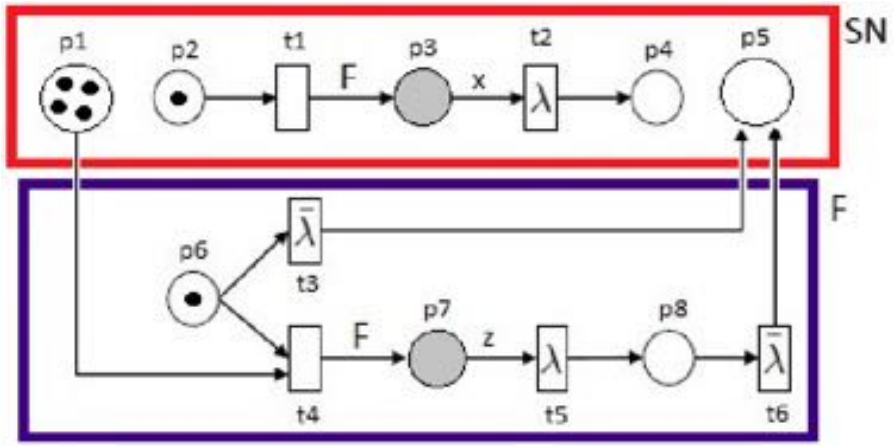


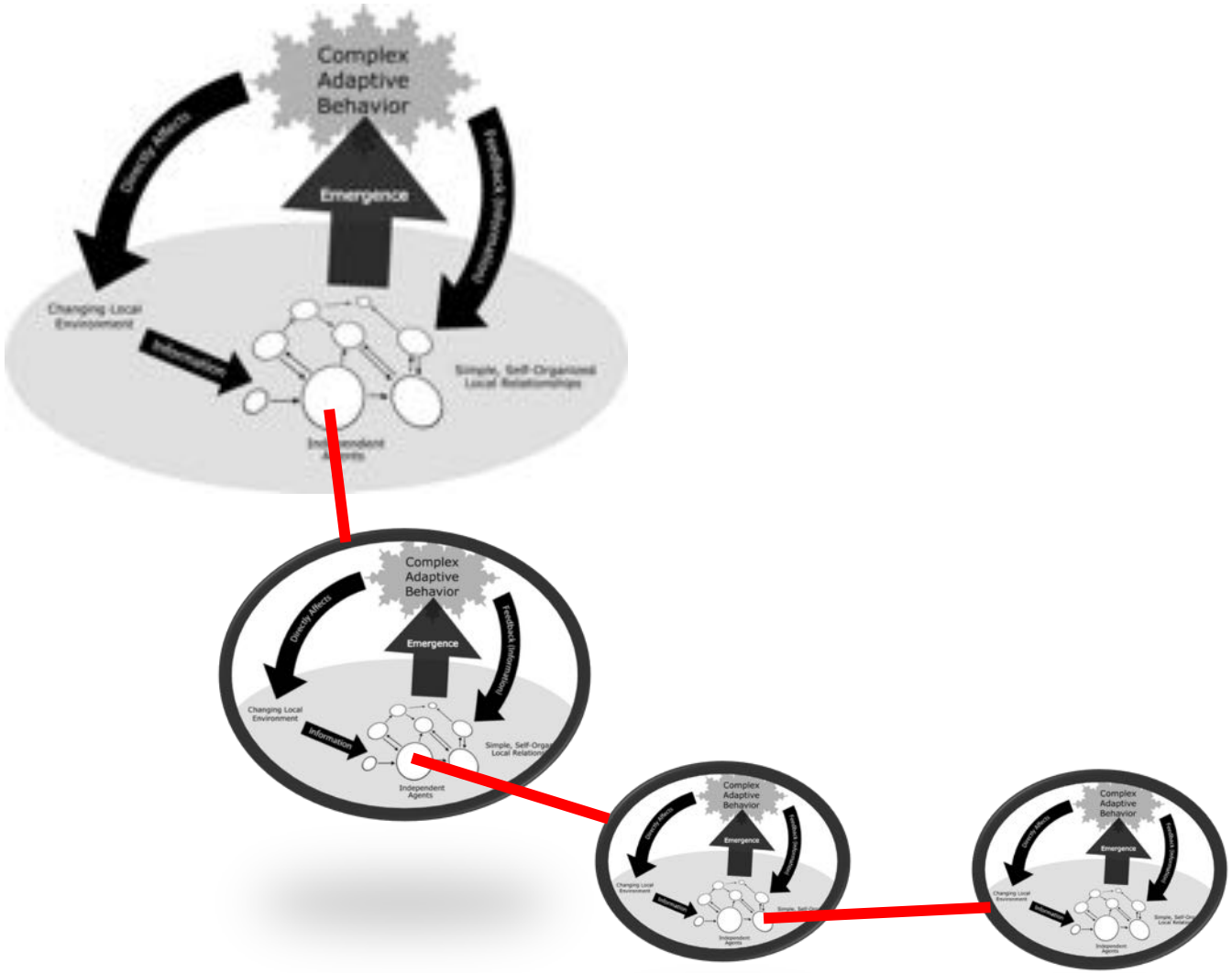



Enabling | **Delay** | **Firing**



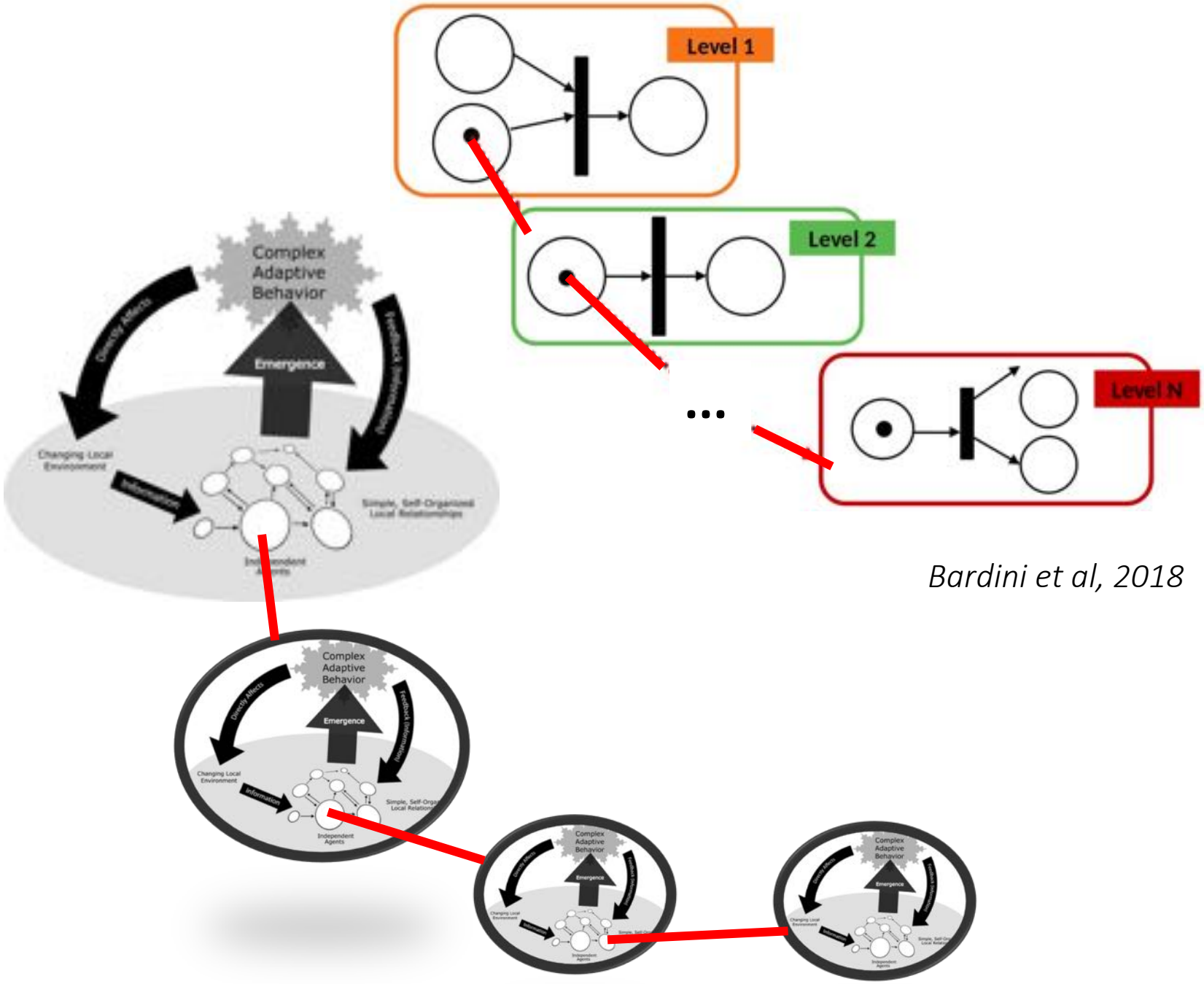

Petri Nets are visual, mathematically defined and executable. Expressing timing, and stochasticity.

# Nets-within-nets




NWNs express **recursively nested** levels, **encapsulation** and **selective communication**.

Supporting **dynamic** hierarchies and objects.



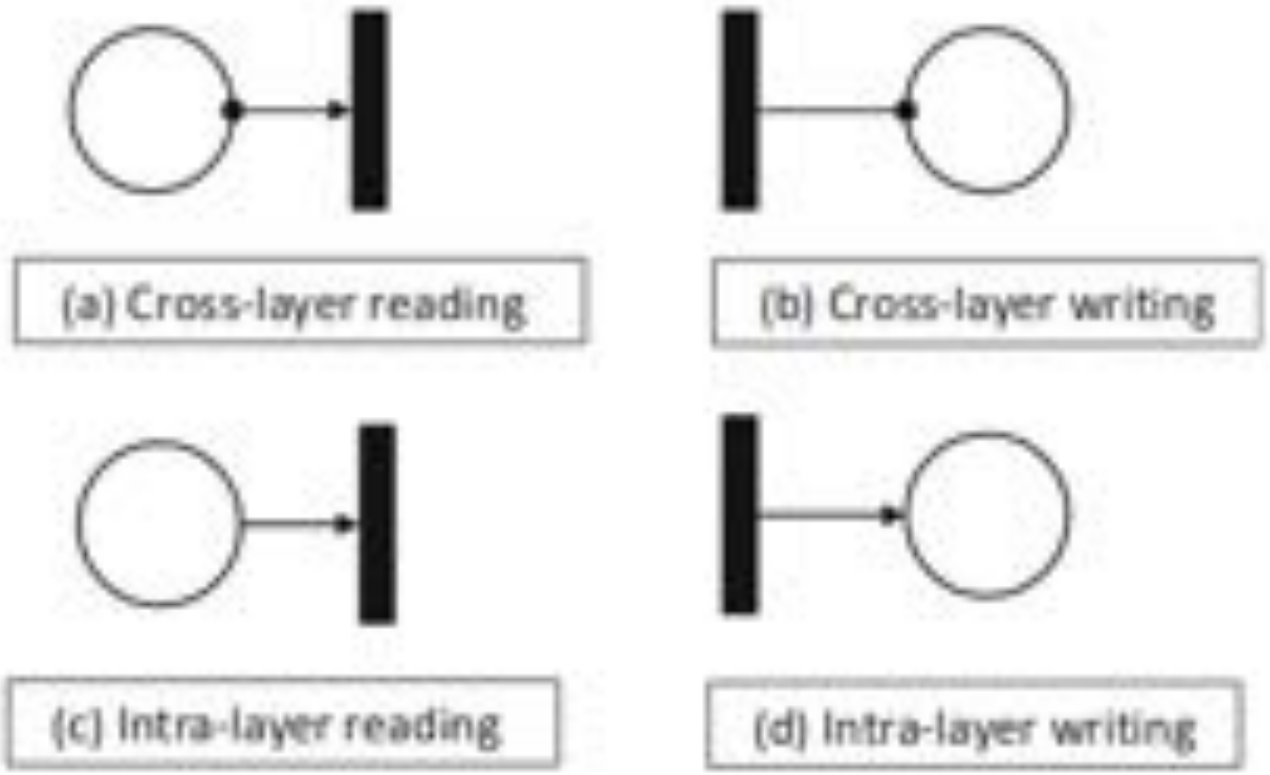

*Bardini et al, 2018*

# Nets-within-nets

NWNs express **recursively nested** levels, **encapsulation** and **selective communication**.

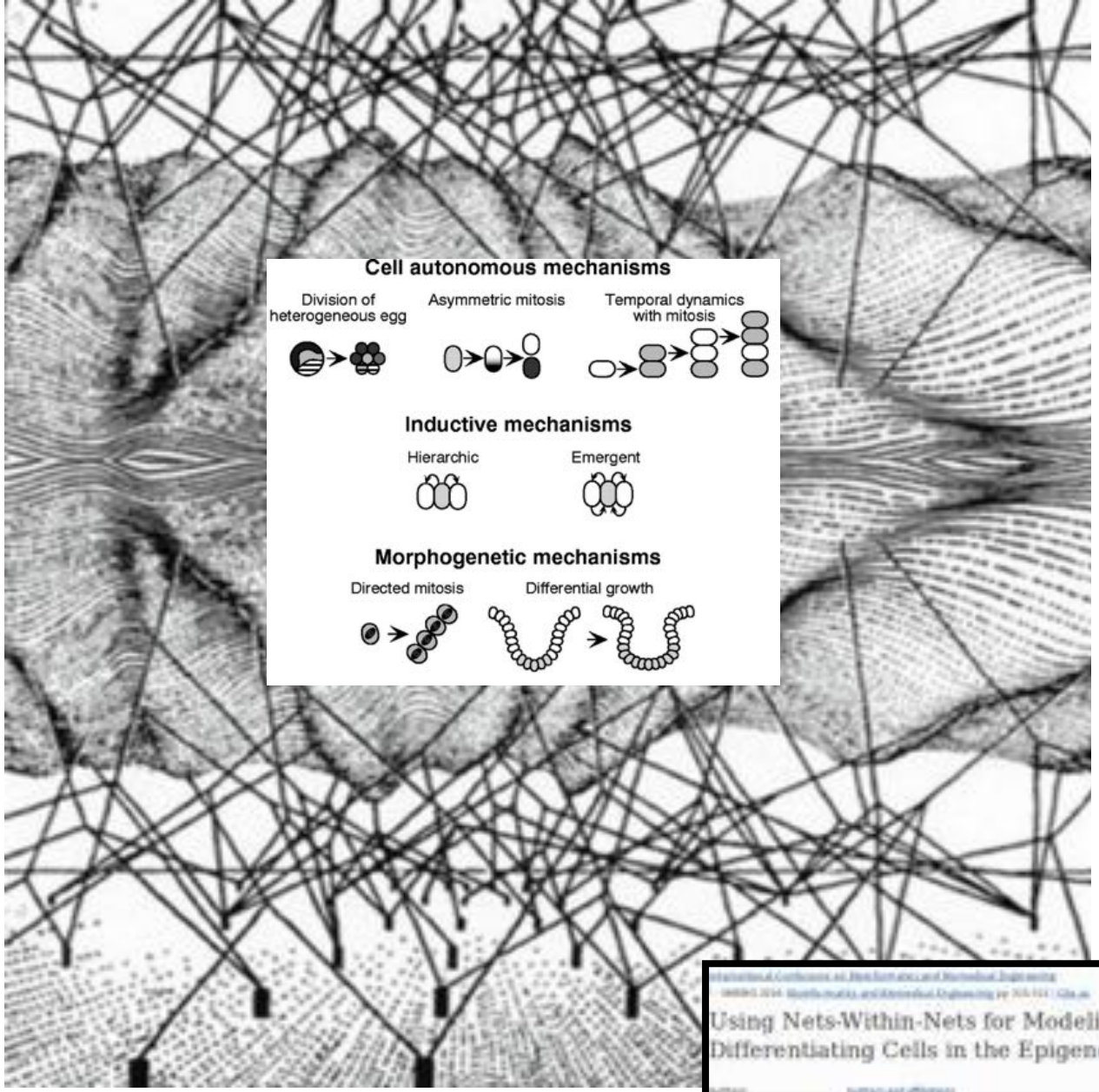
Supporting **dynamic** hierarchies and objects.

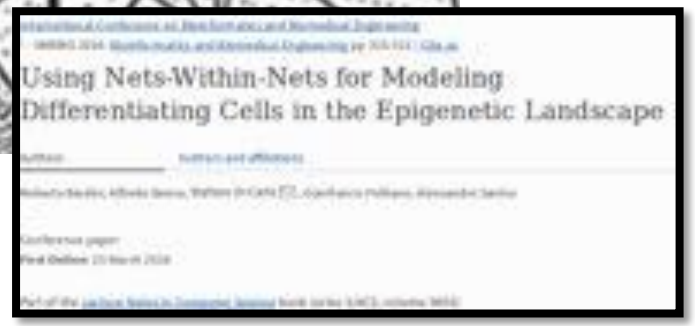
# NWNs communication styles




Communication channels **read** or **write** information or resources within or across levels.

*Bardini et al, 2018*





Using Nets-Within-Nets for Modeling Differentiating Cells in the Epigenetic Landscape

*Adapted from Salazar et al, 2003*

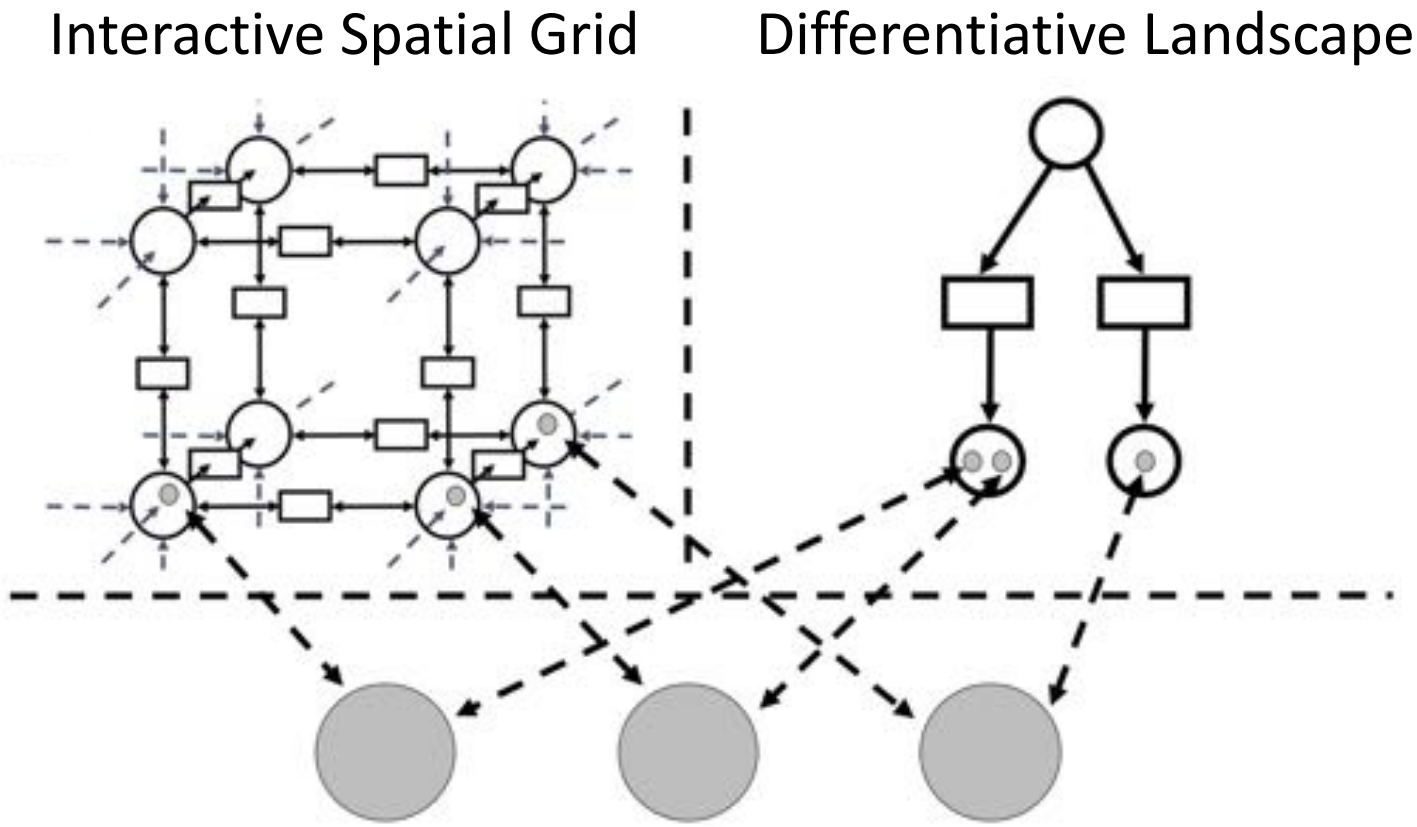
*Noble, 2015 (modified from Waddington, 1957)*

Combined basic mechanisms make a complex landscape

The goal is to **model** spatiality-mediated local interactions at different levels and the **dynamic hierarchy** of regulations they belong to...

# Morphogenetic patterns emerge

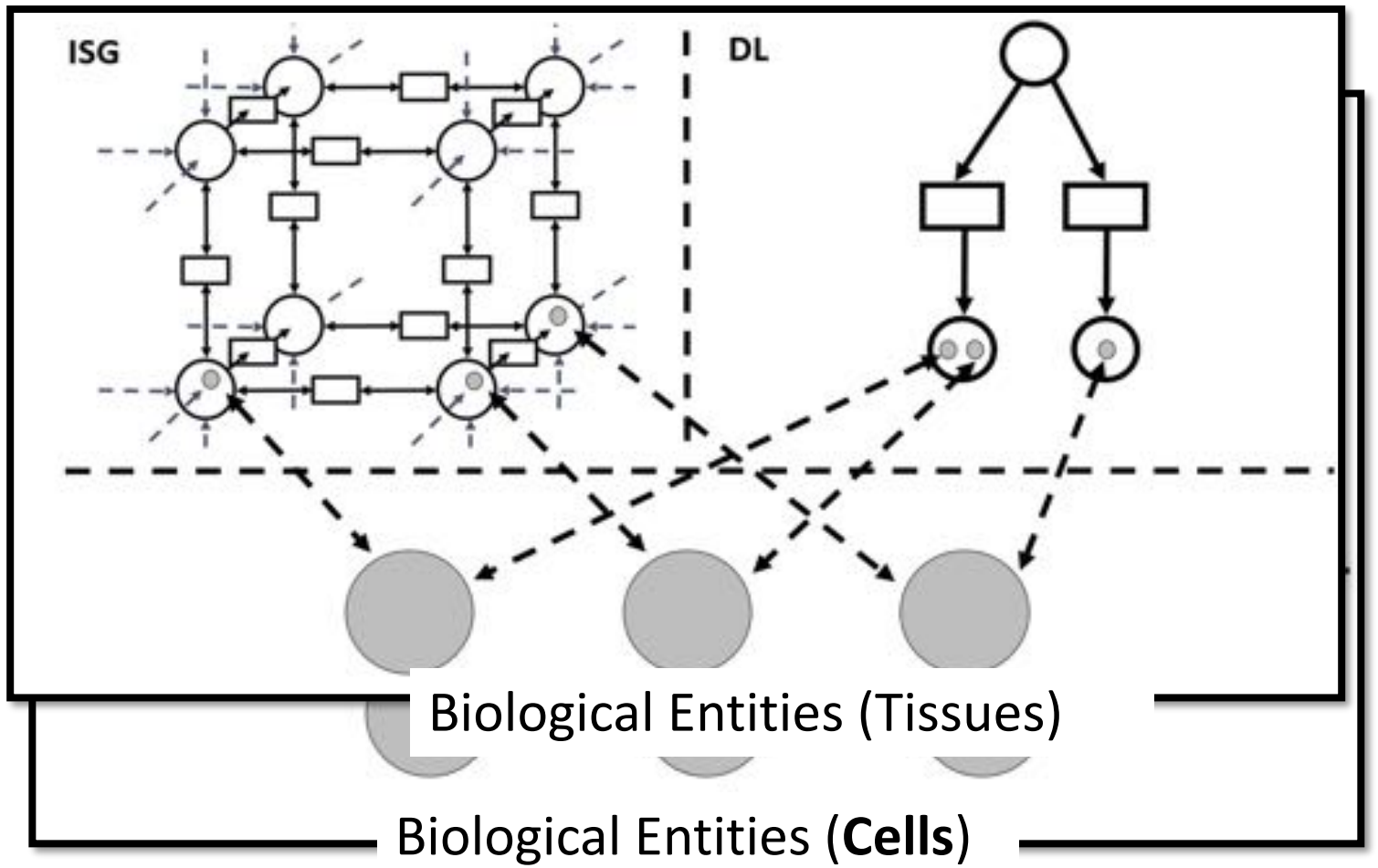
...to **simulate morphogenetic pattern formation**, considering **architectural and phenotype complexity**.



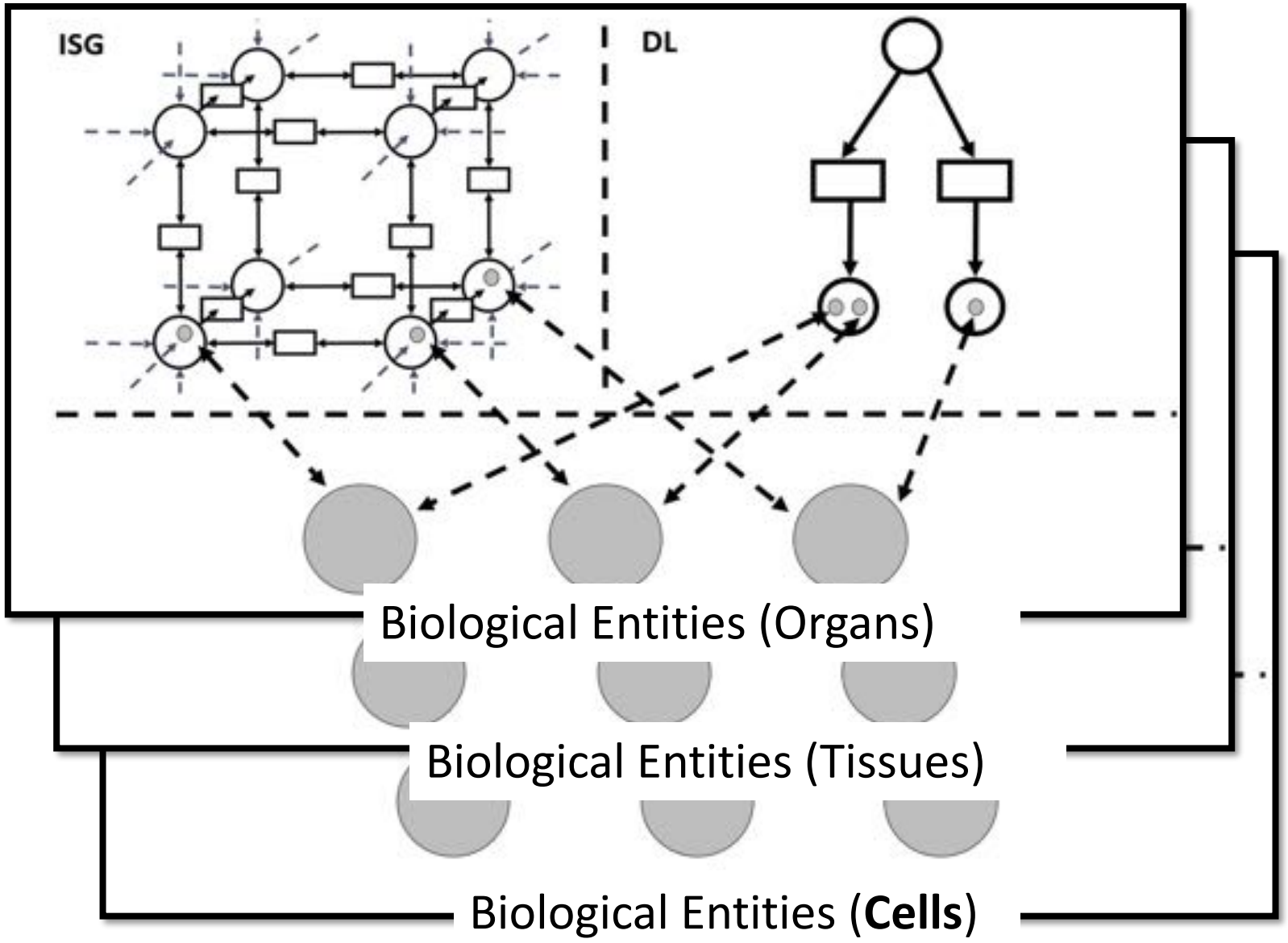

# A multi-level and multi-context modeling approach

Making the regulation **landscape explicit, mediating** functional **interactions**...

# A multi-level and multi-context modeling approach

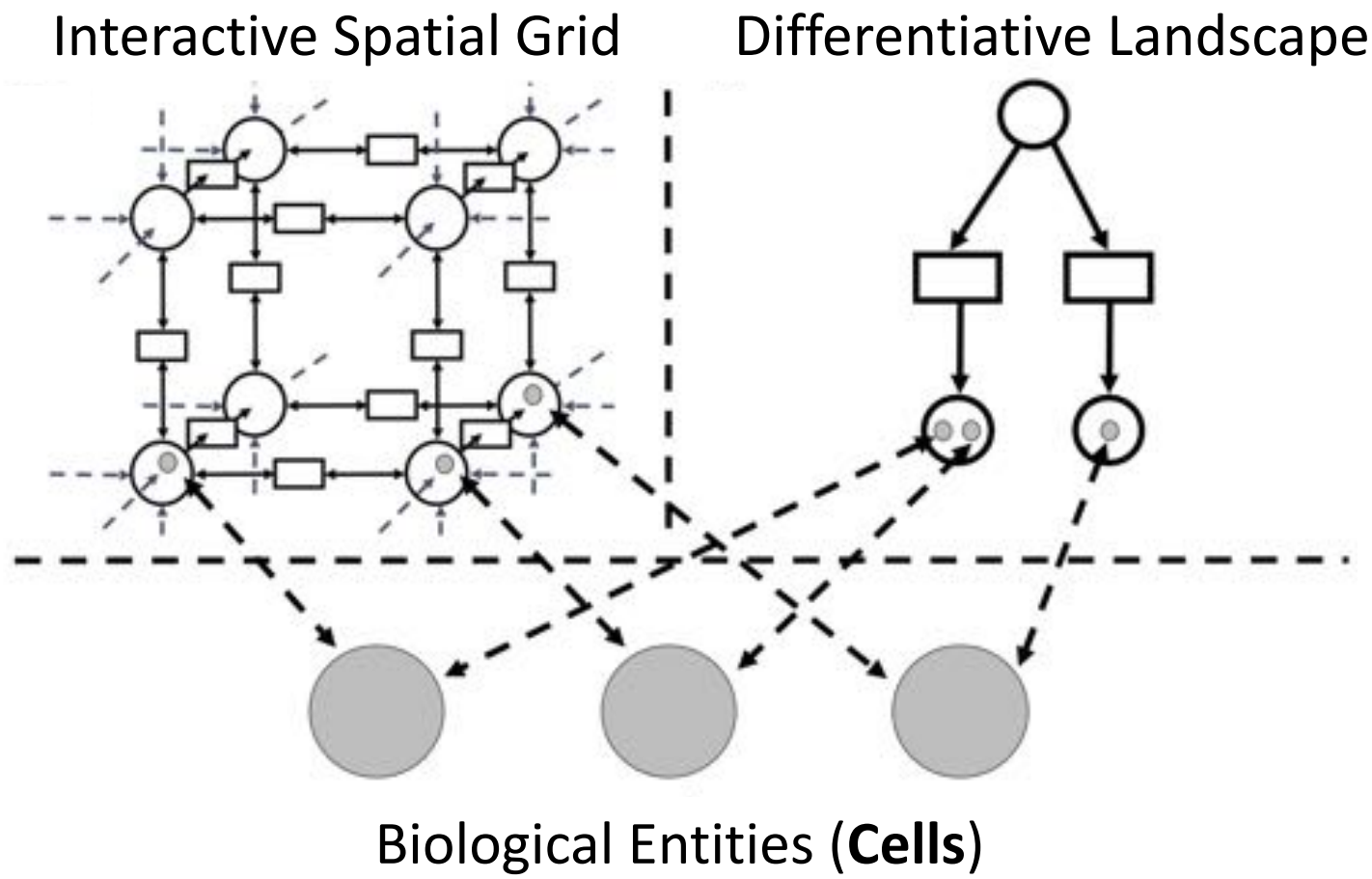



...over multiple system levels.




# A multi-level and multi-context modeling approach

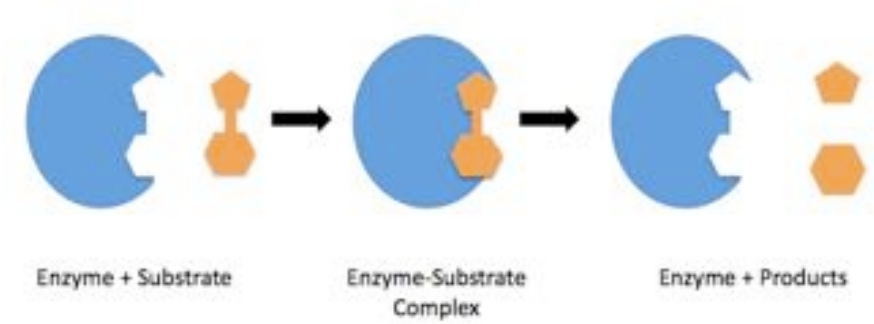
...over multiple system levels.

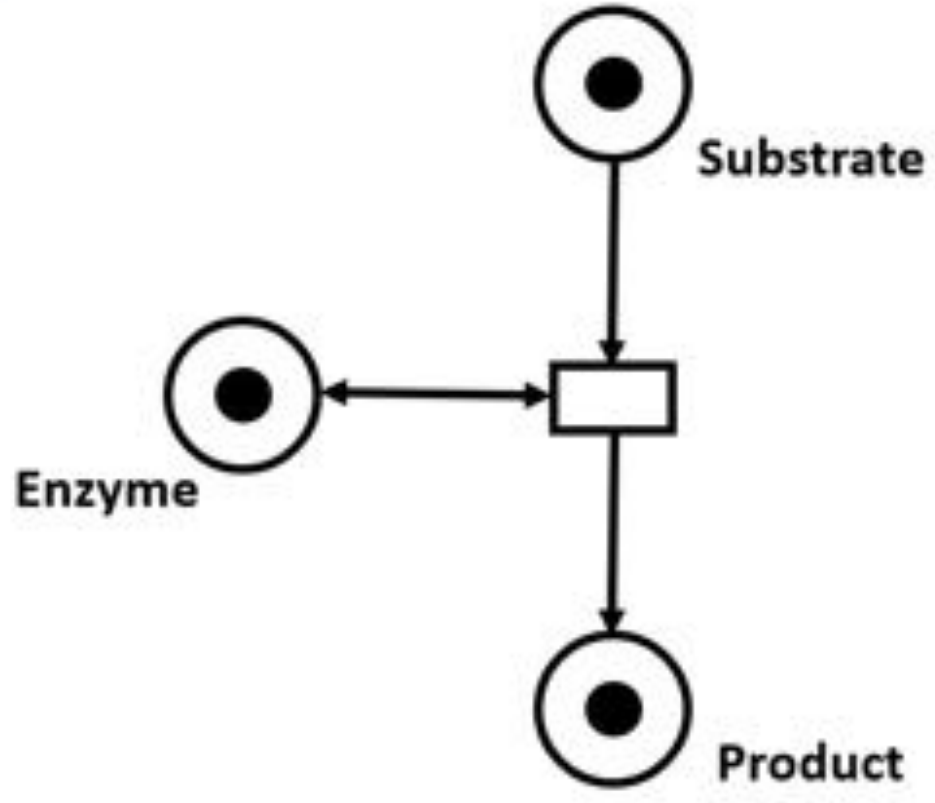



# Basic building blocks for local interactions

Contexts have specific biological **semantics**, and are **consistent** with each other. Sample building blocks provide examples of the modeled basic mechanisms.

# Cells building blocks - enzymatic reaction



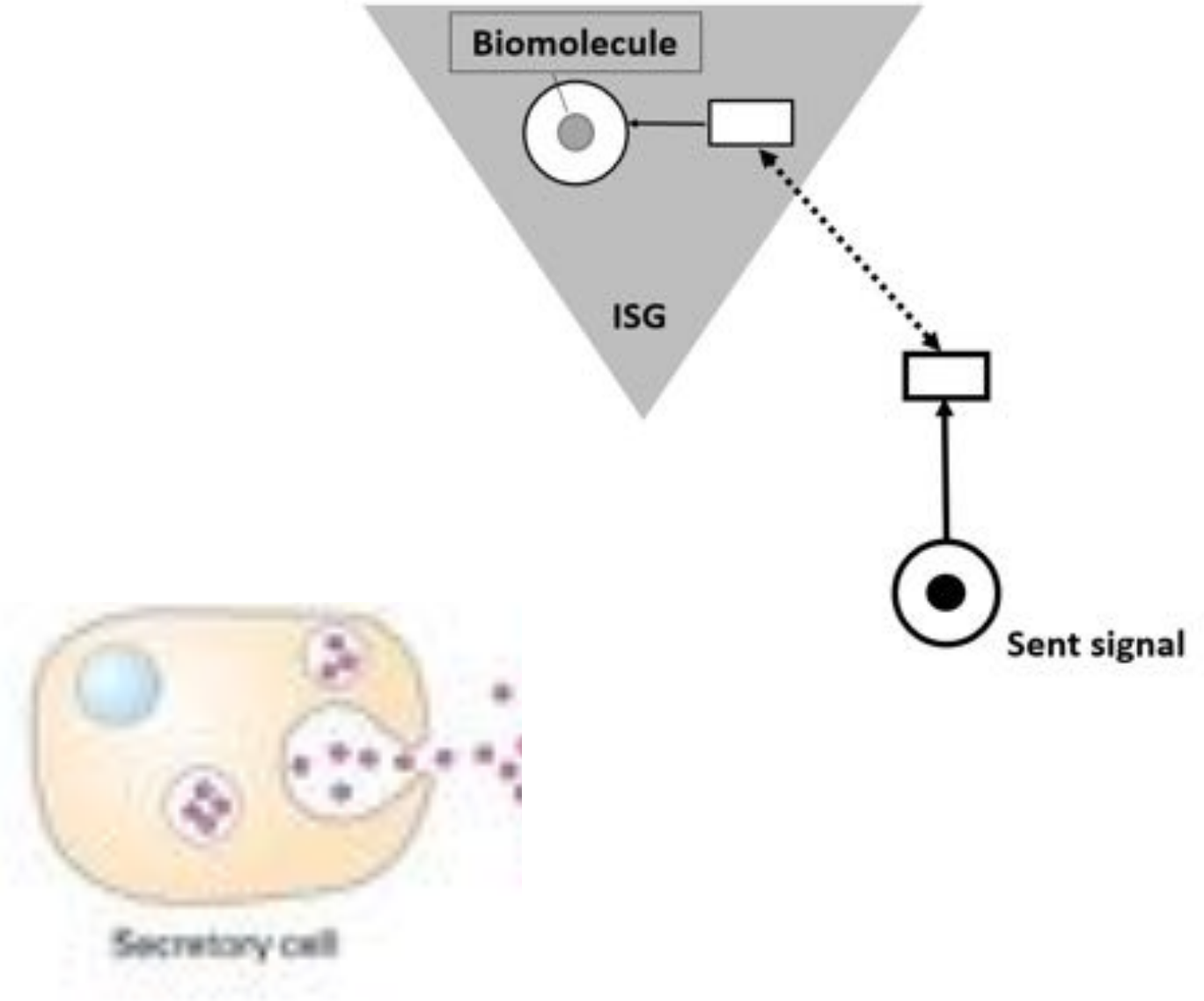




Black tokens: discrete quantity of molecules.

Places: molecular species and states.

Transitions: bioprocesses.

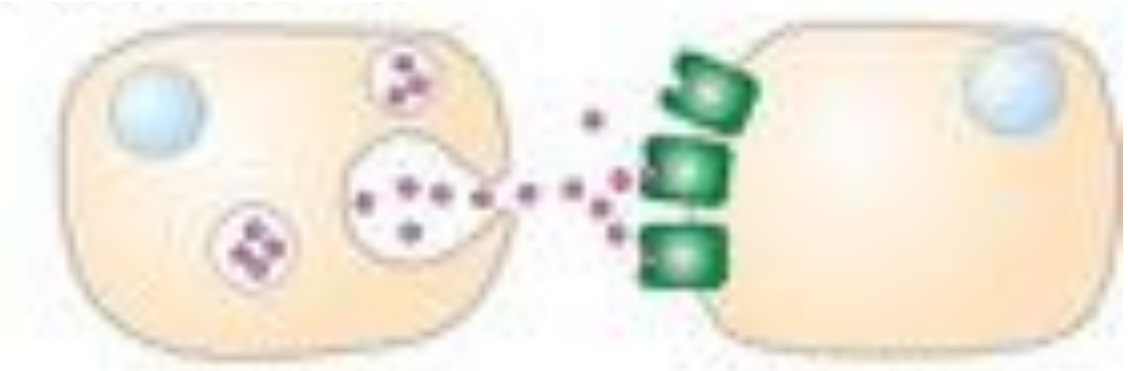
# Cells building blocks - signal sending

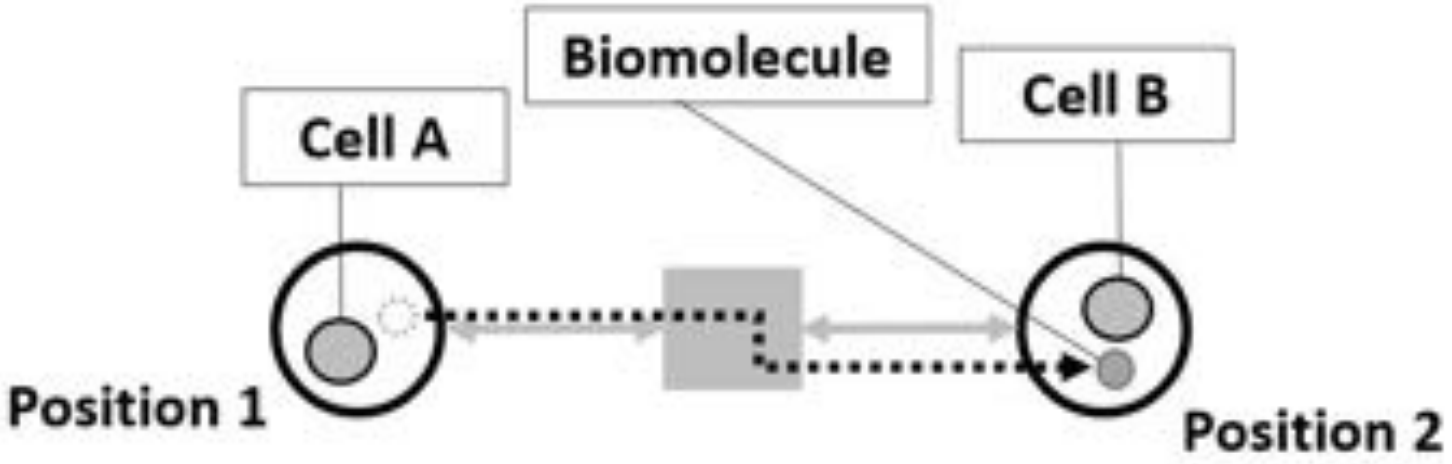



Black tokens: discrete quantity of signal in the Cell model.

Colored tokens: discrete quantity of signal in the ISG, and their identity.

Communication channel: passage of the signal across the cell membrane (writing resources to the ISG).





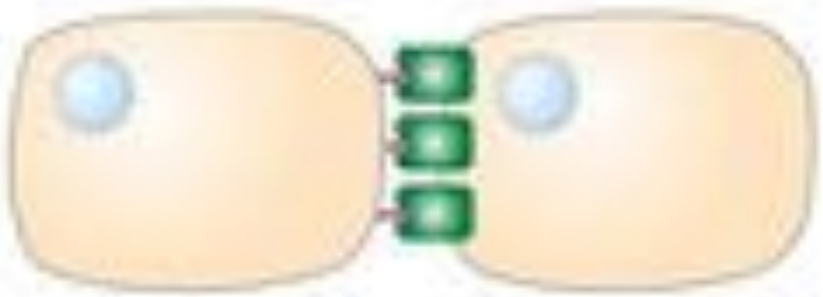

# ISG building blocks – molecular flow

Colored tokens: discrete quantity of molecules, and their identity.

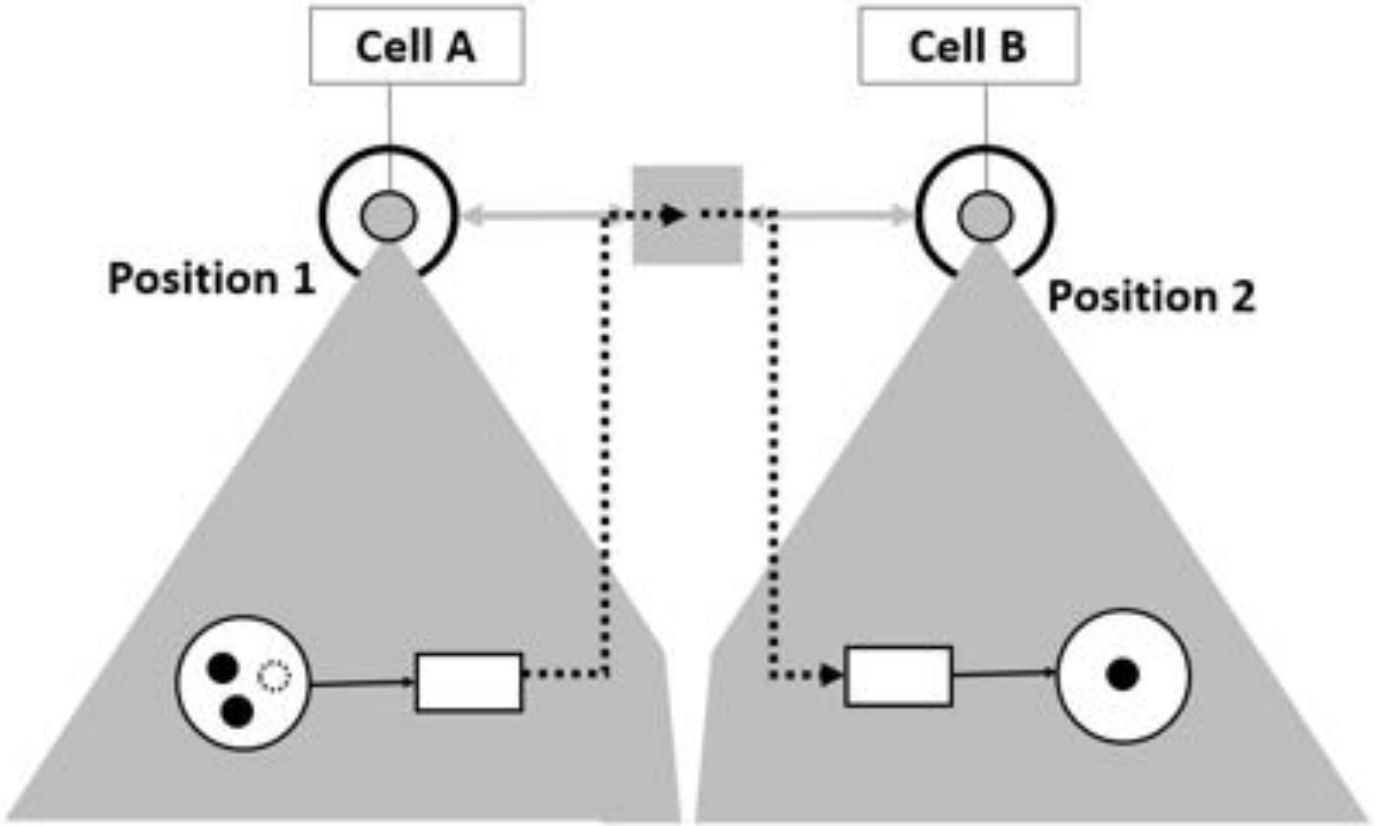
Net tokens: Cell models.

Places: sub-portions of space.

Transitions: spatiality-mediated interactions between Cell models living in neighboring sub-portions of space.



Proximity in the ISG enables interaction, actualizing the neighborhood relation




## ISG building blocks – neighbor communication

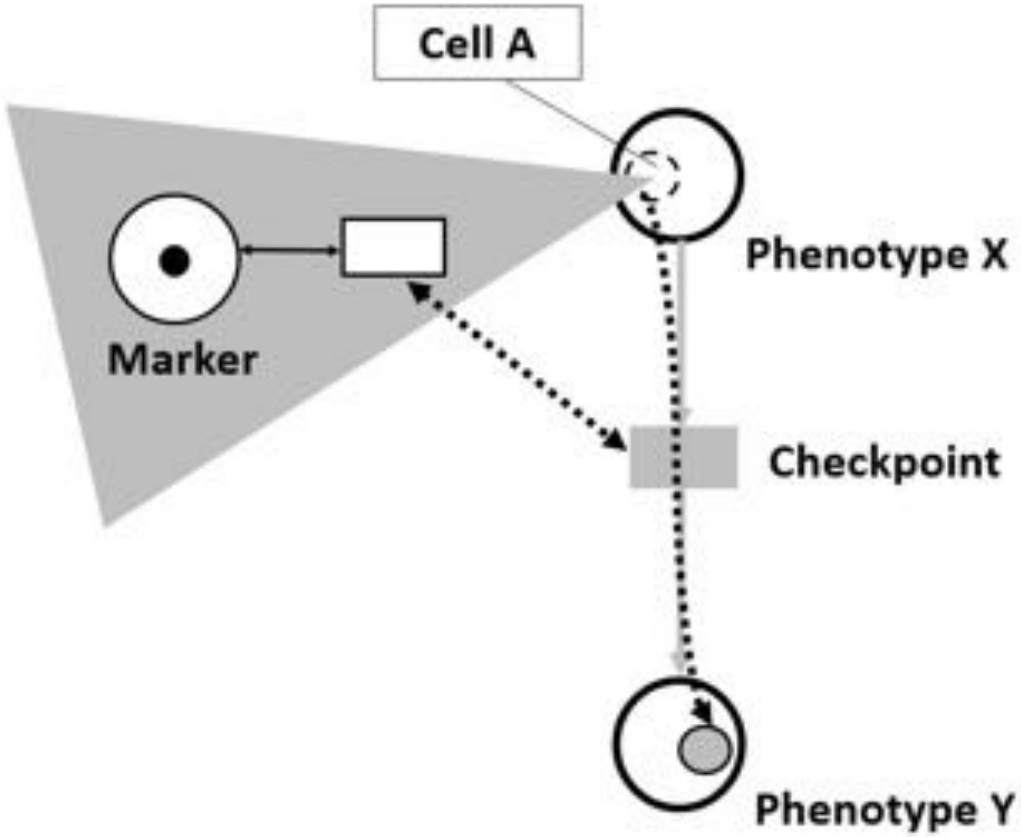
Black tokens: discrete quantity of signal in a Cell model.

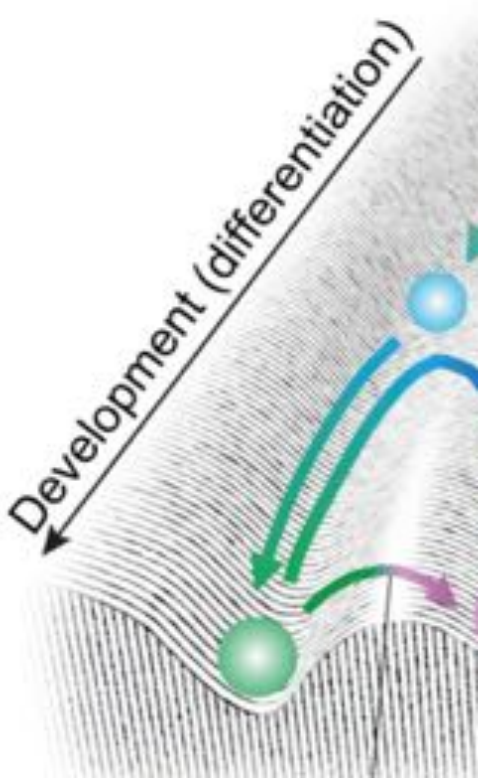
Colored tokens: discrete quantity of signal with their identity in the ISG.

Net tokens: Cell models.

Communication channels: passage of the signal across the cell membrane (writing and reading resources to and from the ISG).

# DL building blocks – differentiative step



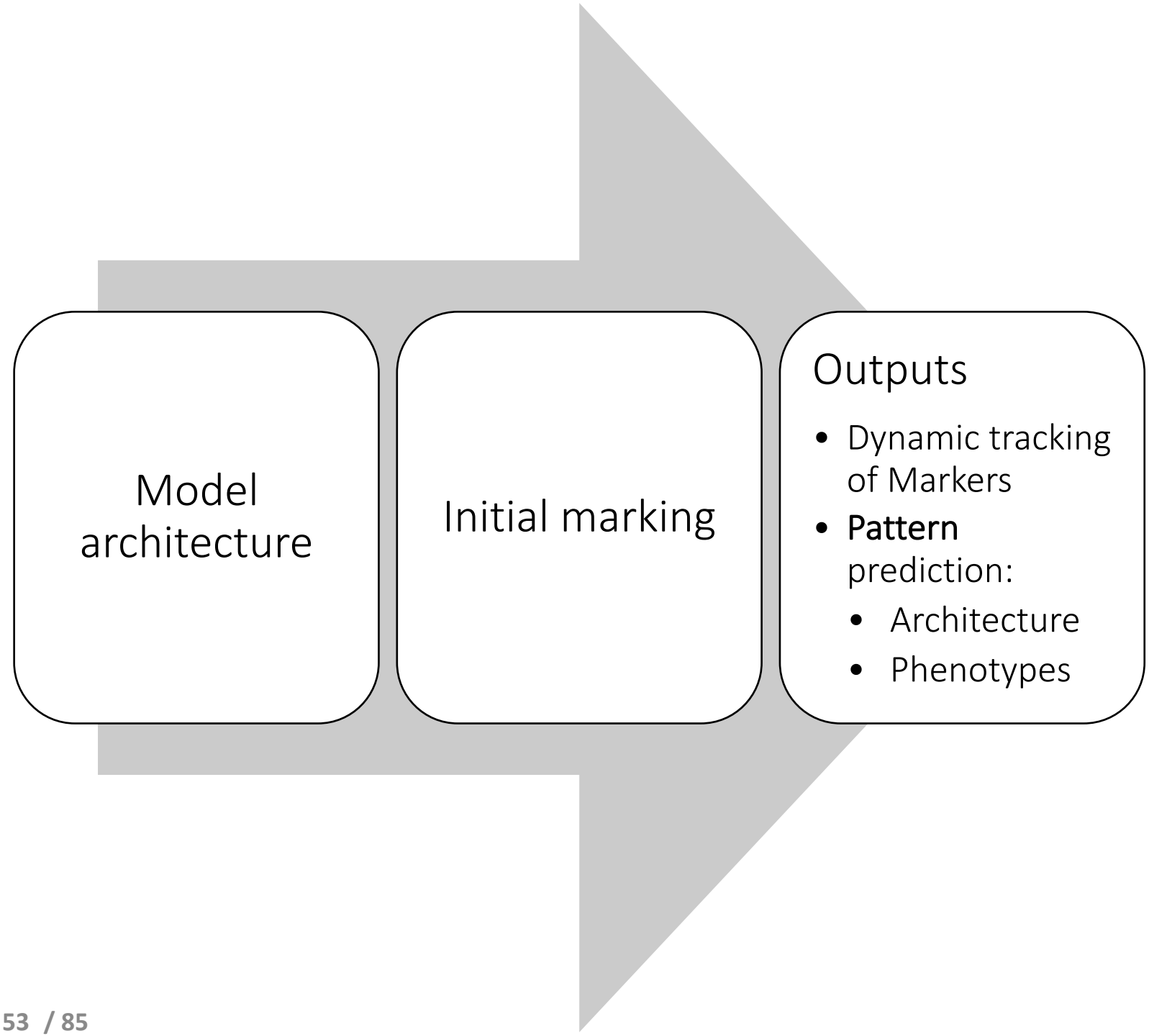




Black tokens: discrete quantity of Marker molecules in Cell models.

Net tokens: Cell models.
Places: phenotypes or states.

Transitions: Checkpoints evaluating phenotype changes by Markers and moving Cells accordingly.

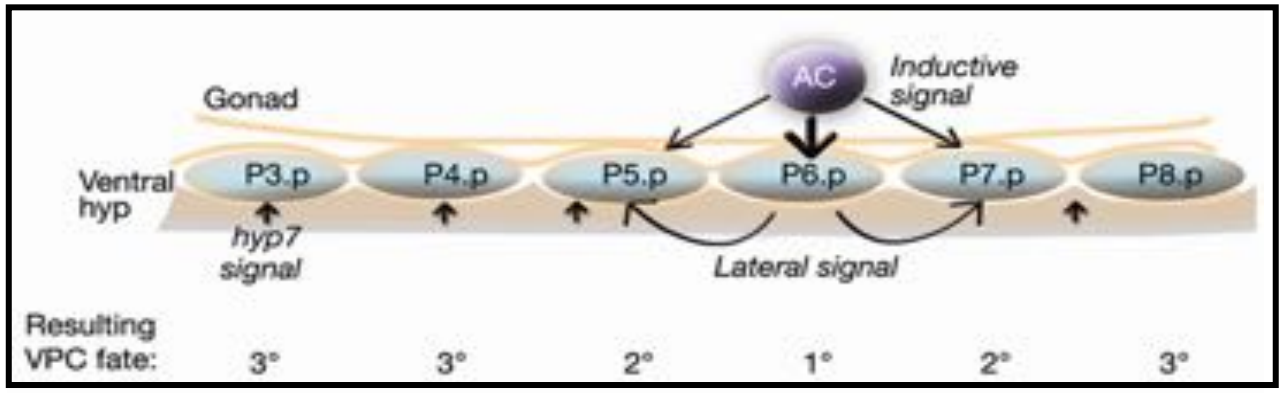
Communication channel: access to Marker by DL (reading information from the Cell).

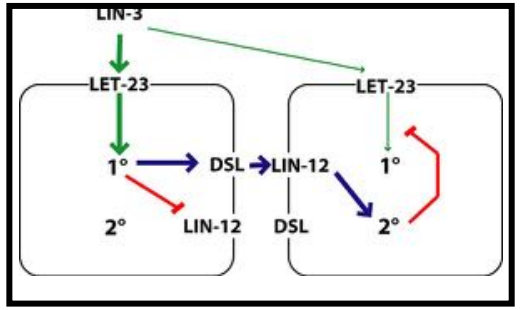



# Simulations

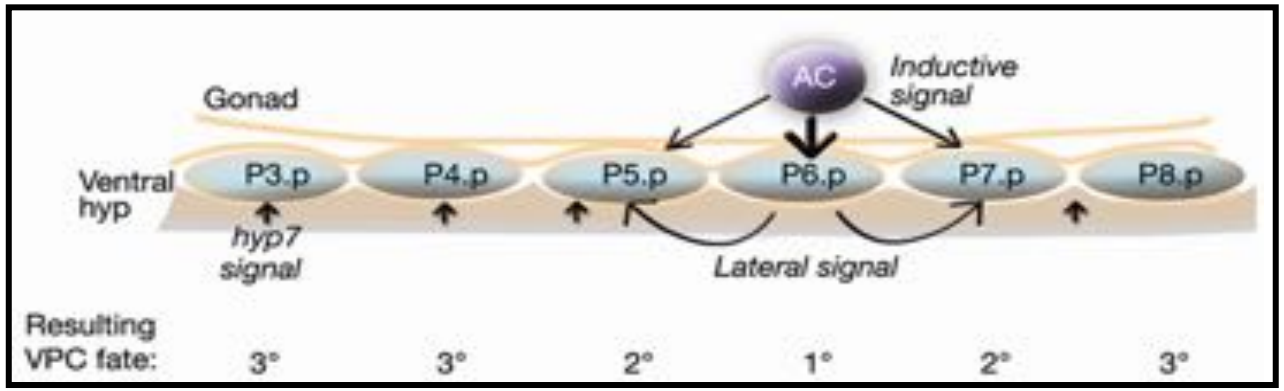
Stochastic simulations express process, architectural and phenotype complexity.

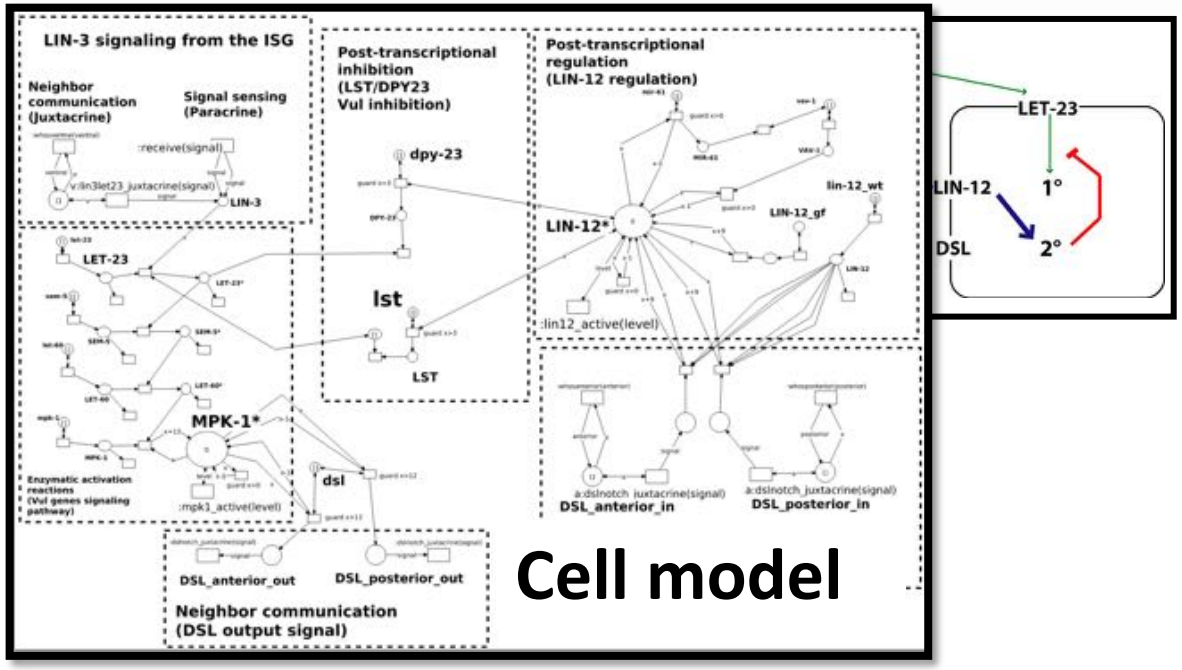
# Application examples




# VPC specification in C. Elegans

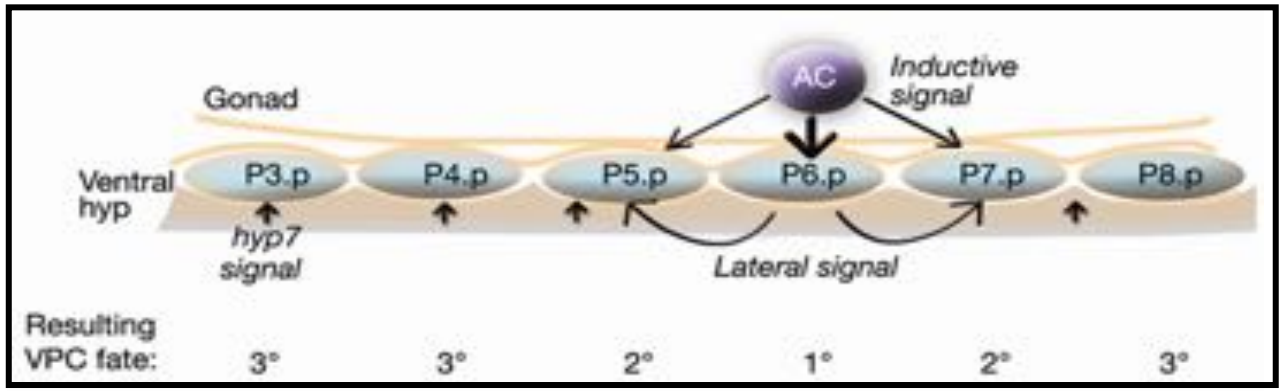


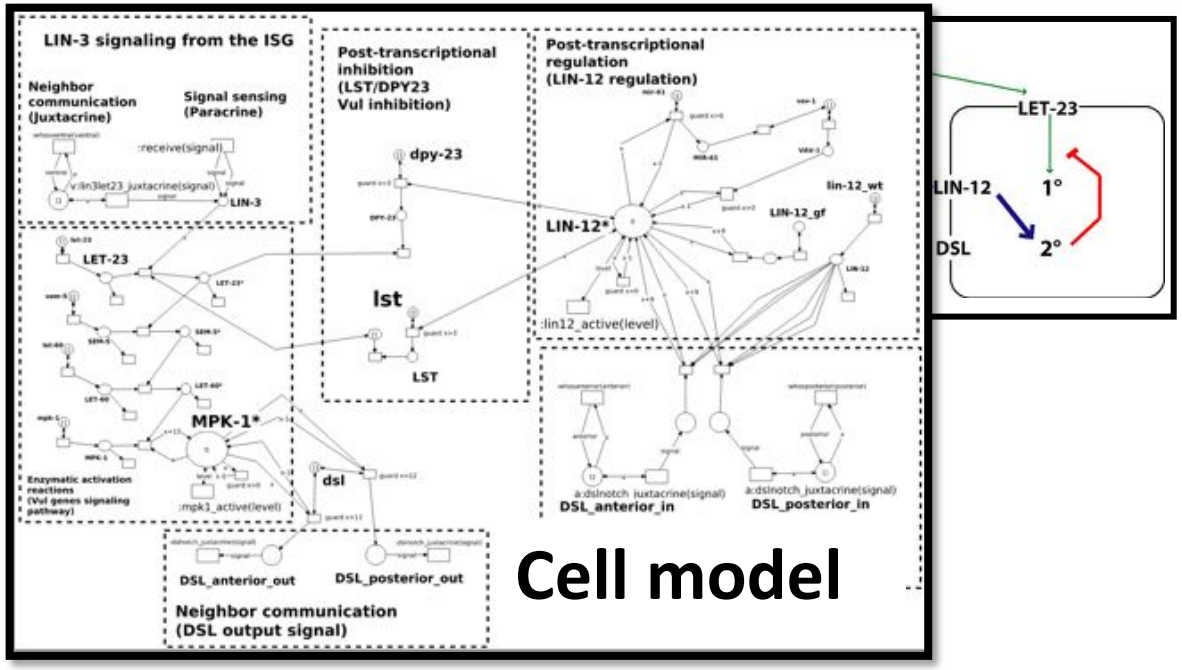







# VPC specification in C. Elegans

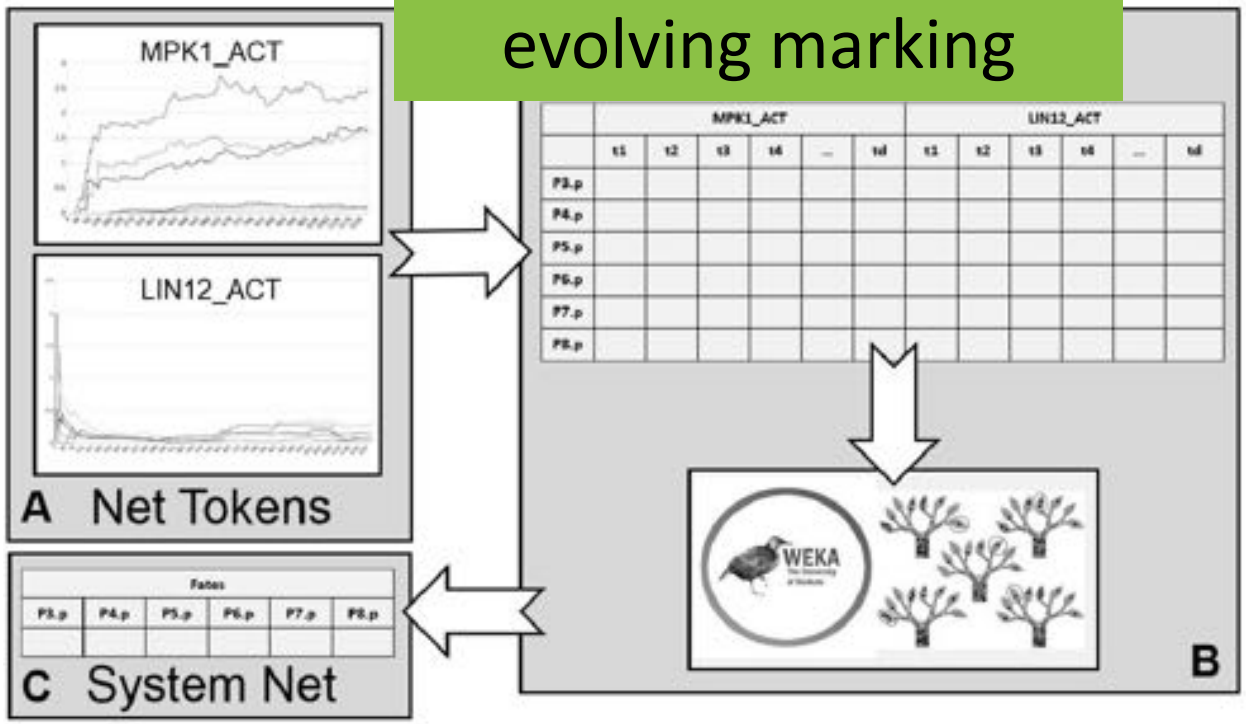




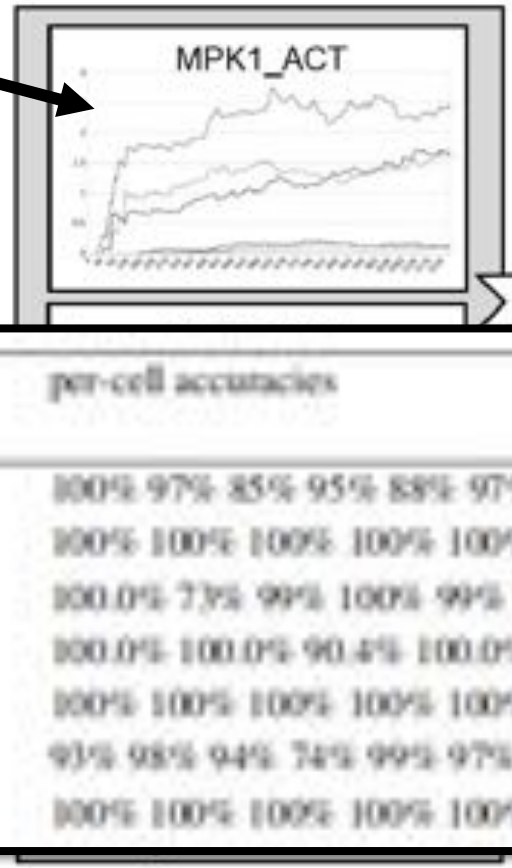


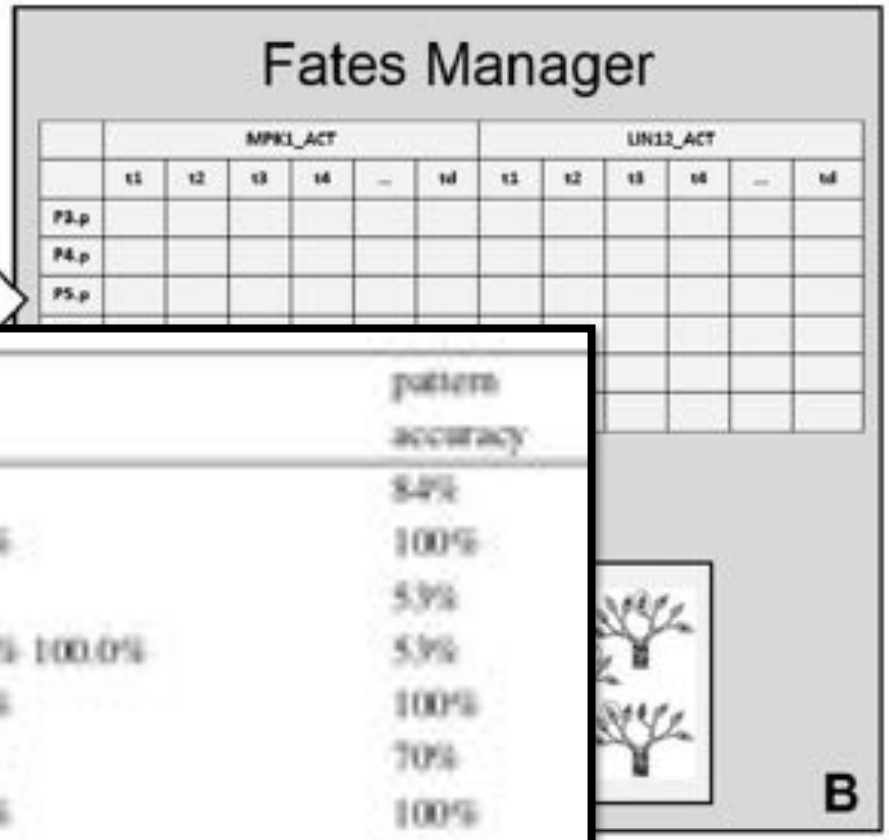
The DL computes cell fates from Marker evolving marking




# VPC specification in C. Elegans

Simulations output
Markers traces
and a 1D spatial
pattern of cell fates

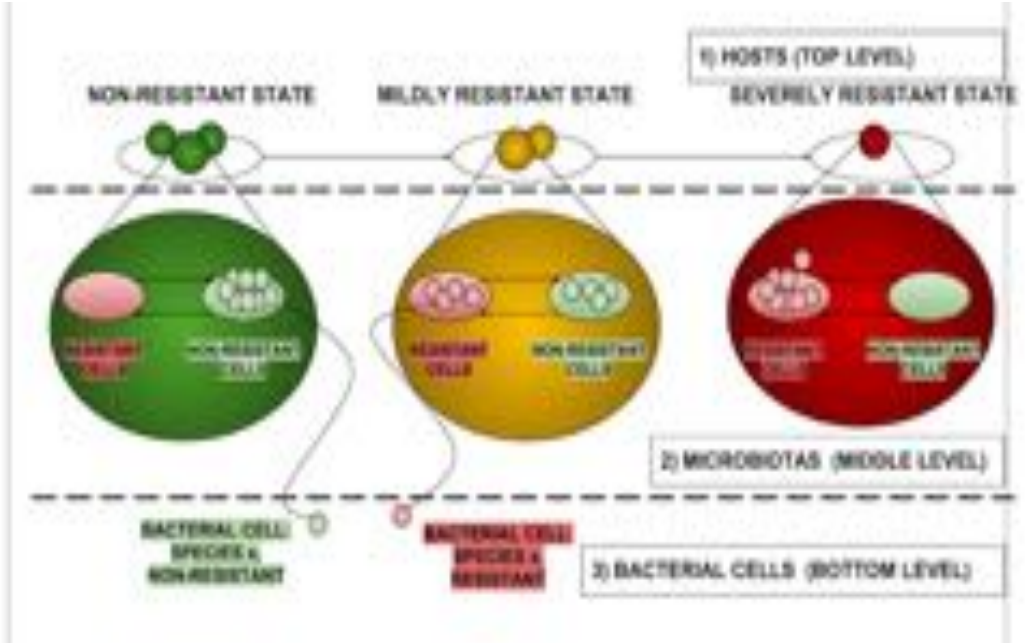


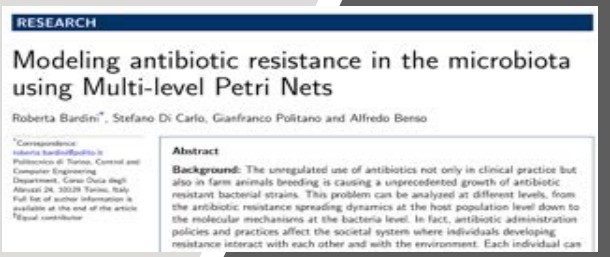

| experiment | P(3-5).p pattern | per-cell accuracies | pattern accuracy |
|---|---|---|---|
| wt | 3 3 2 1 2 3 | 100% 97% 85% 95% 88% 97% | 84% |
| ΔCab | 3 3 3 3 3 3 | 100% 100% 100% 100% 100% 100% | 100% |
| lst4ko | 3 3 1 1 1 3 | 100.0% 73% 99% 100% 99% 71% | 5.9% |
| lin12ko | 3 1 1 1 3 3 | 100.0% 100.0% 90.4% 100.0% 92.2% 100.0% | 5.9% |
| lin12d | 2 2 2 1/2 2 2 | 100% 100% 100% 100% 100% 100% | 100% |
| lin15ko | 1/2 1/2 1/2 1 1/2 1/2 | 93% 98% 94% 74% 99% 97% | 70% |
| Vulko | 3 3 3 3 3 3 | 100% 100% 100% 100% 100% 100% | 100% |

# VPC specification in C. Elegans

# Flexibility of the approach: no ISG and two "DL" levels




# Antibiotic resistance in the microbiota


RESEARCH

Modeling antibiotic resistance in the microbiota using Multi-level Petri Nets

Roberta Bardini*, Stefano Di Carlo, Gianfranco Politano and Alfredo Benso

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roberta.bardini@polito.it
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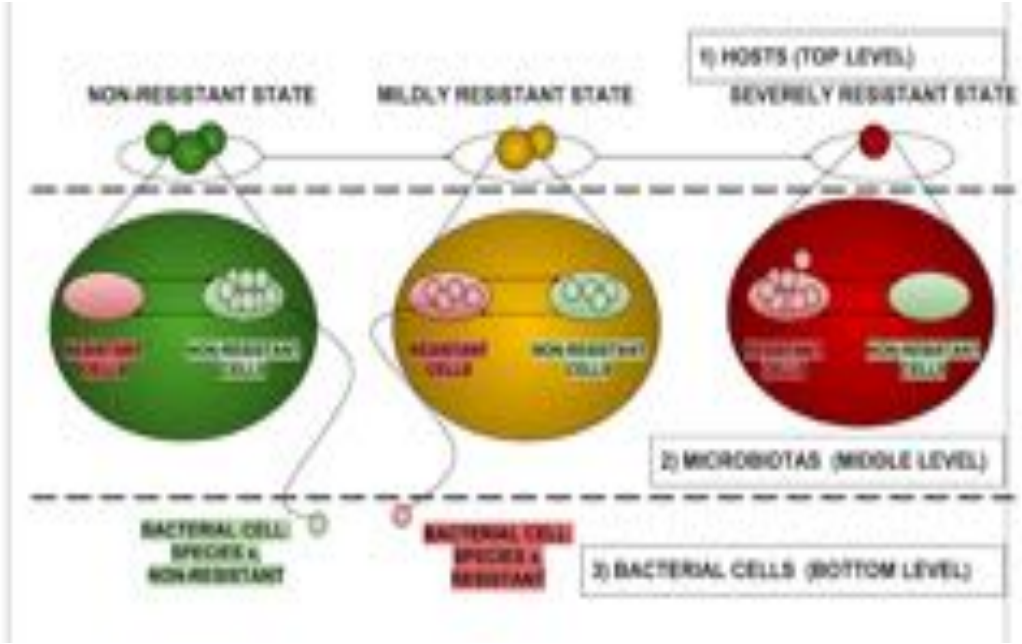
†Equal contributor

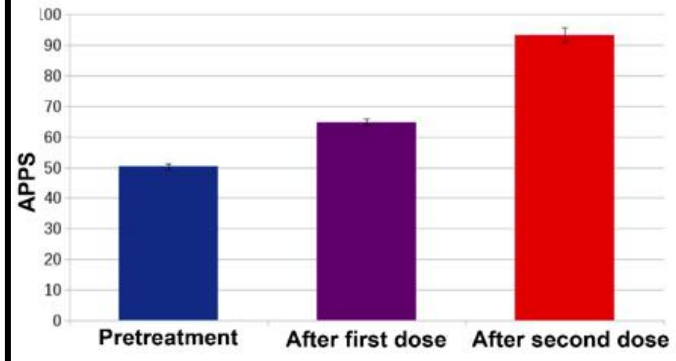
Abstract

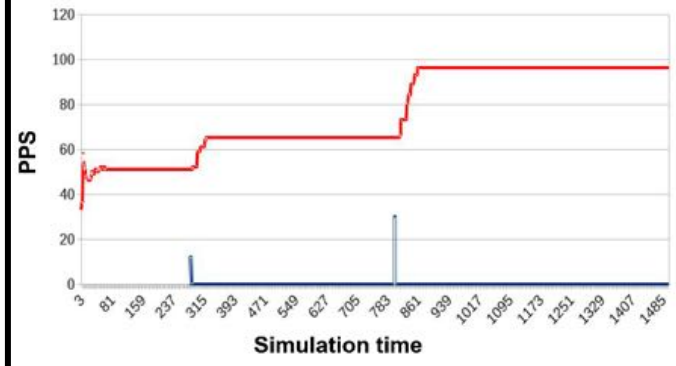
**Background:** The unregulated use of antibiotics not only in clinical practice but also in farm animals breeding is causing a unprecedented growth of antibiotic resistant bacterial strains. This problem can be analyzed at different levels, from the antibiotic resistance spreading dynamics at the host population level down to the molecular mechanisms at the bacteria level. In fact, antibiotic administration policies and practices affect the societal system where individuals developing resistance interact with each other and with the environment. Each individual can

# Simulating different clinical protocols

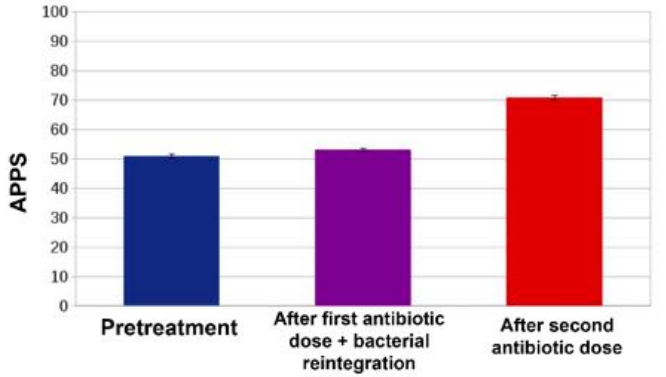


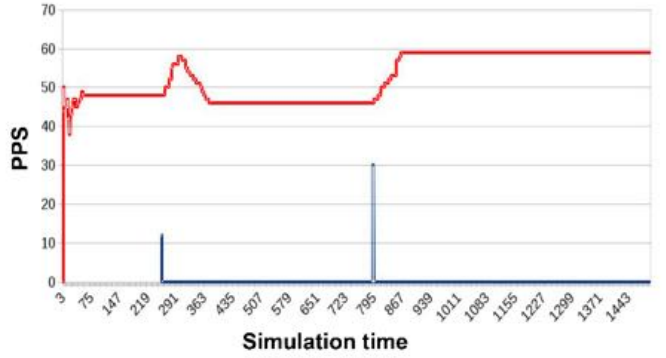

## Antibiotic administration



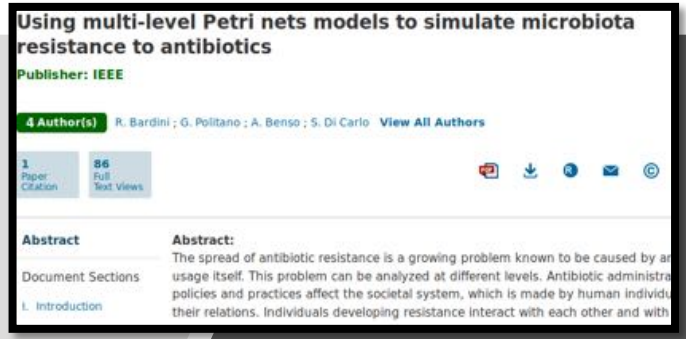




## Antibiotic administration + bacterial reintegration




# Antibiotic resistance in the microbiota


Using multi-level Petri nets models to simulate microbiota resistance to antibiotics

Publisher: IEEE

4 Author(s) R. Bardini ; G. Politano ; A. Benso ; S. Di Carlo View All Authors

1 Paper Citation

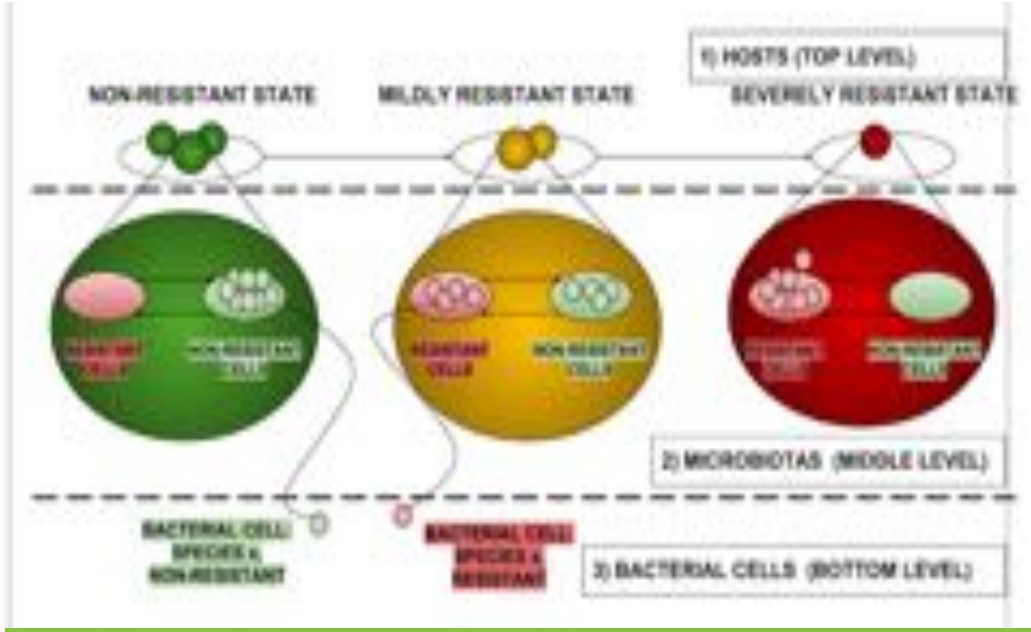
86 Full Text Views

Abstract

Document Sections

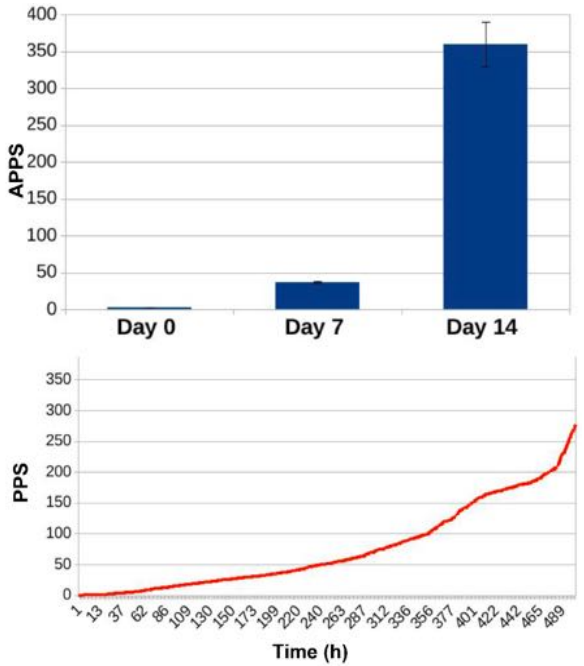
I. Introduction

Abstract:
The spread of antibiotic resistance is a growing problem known to be caused by a usage itself. This problem can be analyzed at different levels. Antibiotic administra policies and practices affect the societal system, which is made by human individu their relations. Individuals developing resistance interact with each other and with

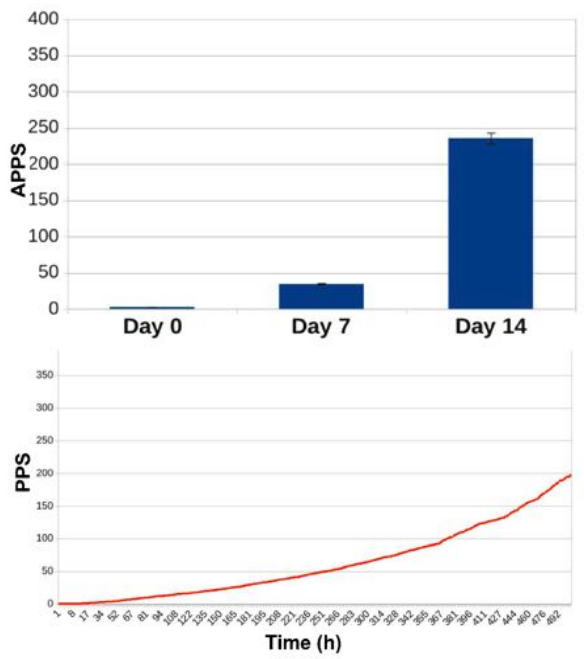



Model composition and information integration

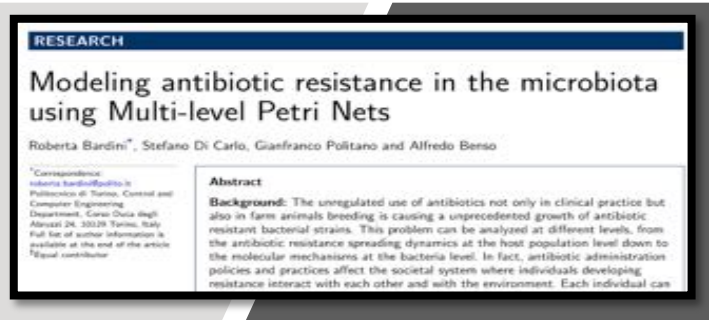
## Antibiotic administration




## Antibiotic administration + bacterial reintegration




# Antibiotic resistance in the microbiota


RESEARCH

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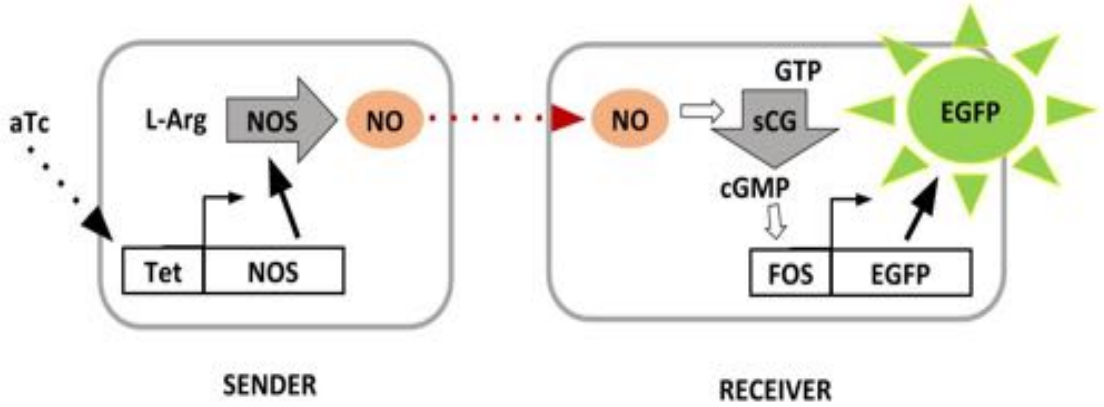
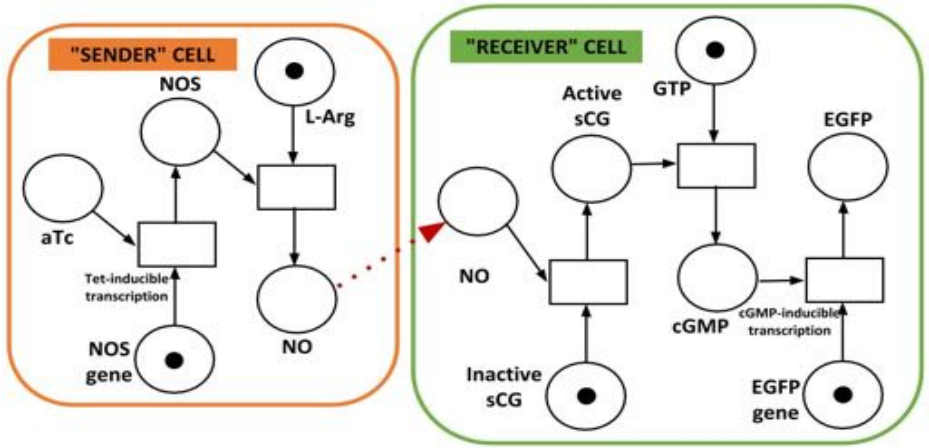
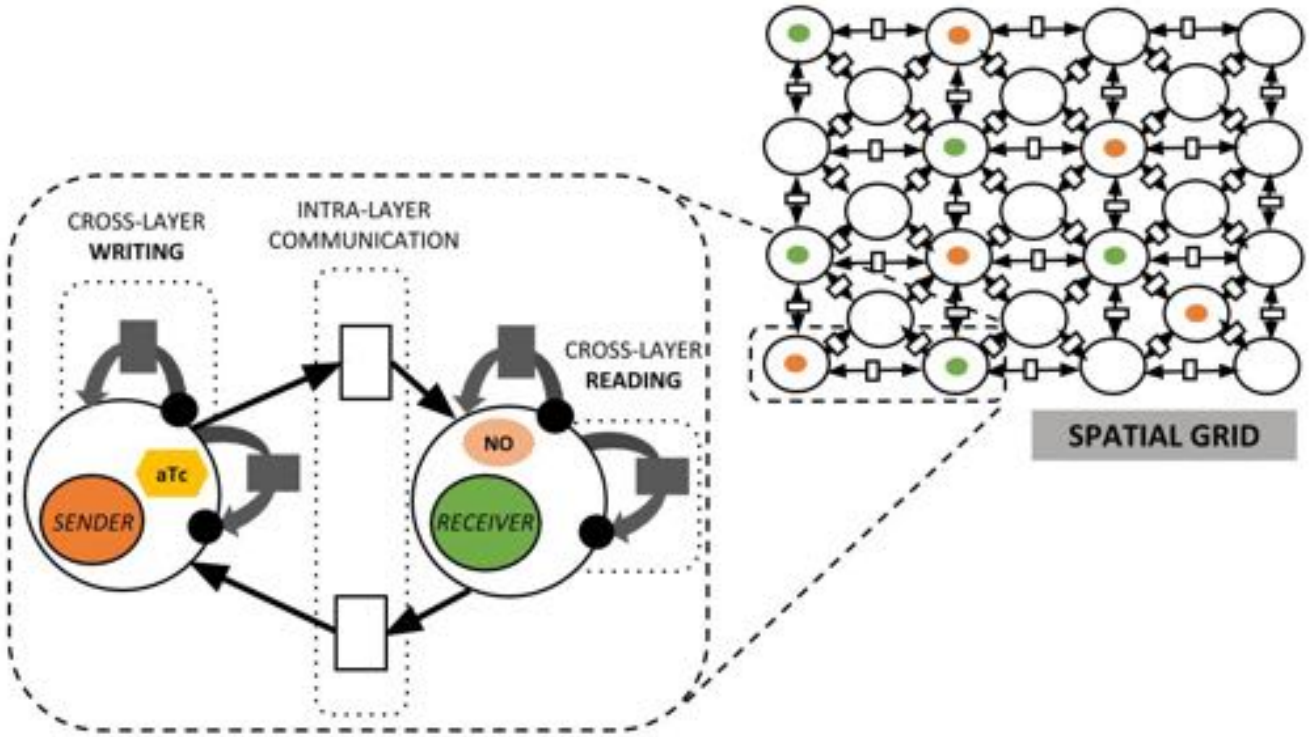
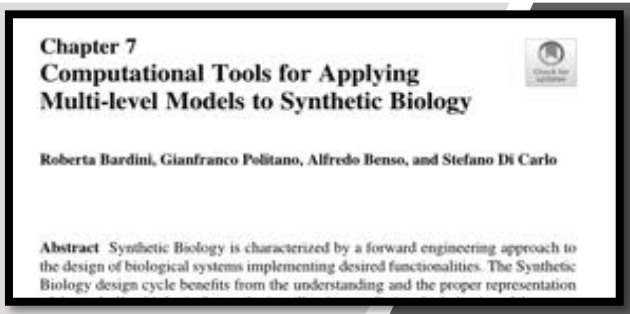



Models can help synthetic designs by handling system complexity



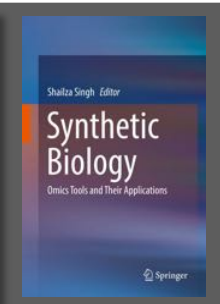

# Synthetic biology, from modules to systems

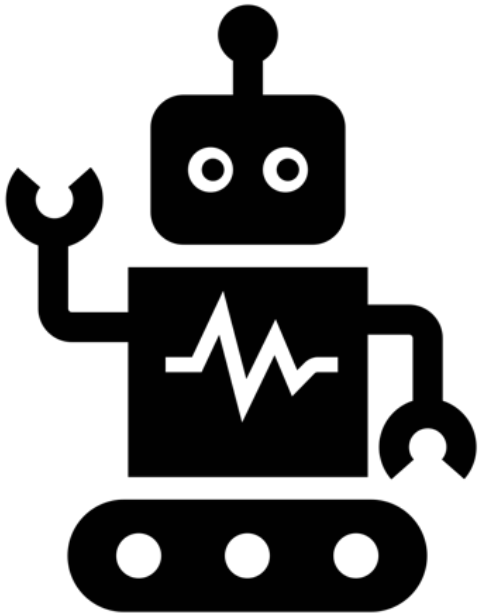


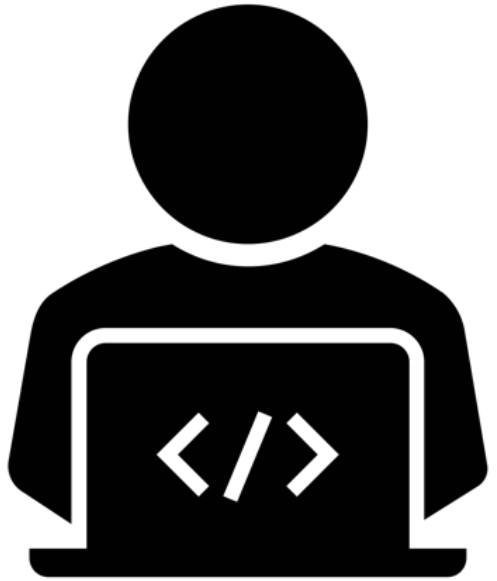
Chapter 7
Computational Tools for Applying Multi-level Models to Synthetic Biology

Roberta Bardini, Gianfranco Politano, Alfredo Benso, and Stefano Di Carlo

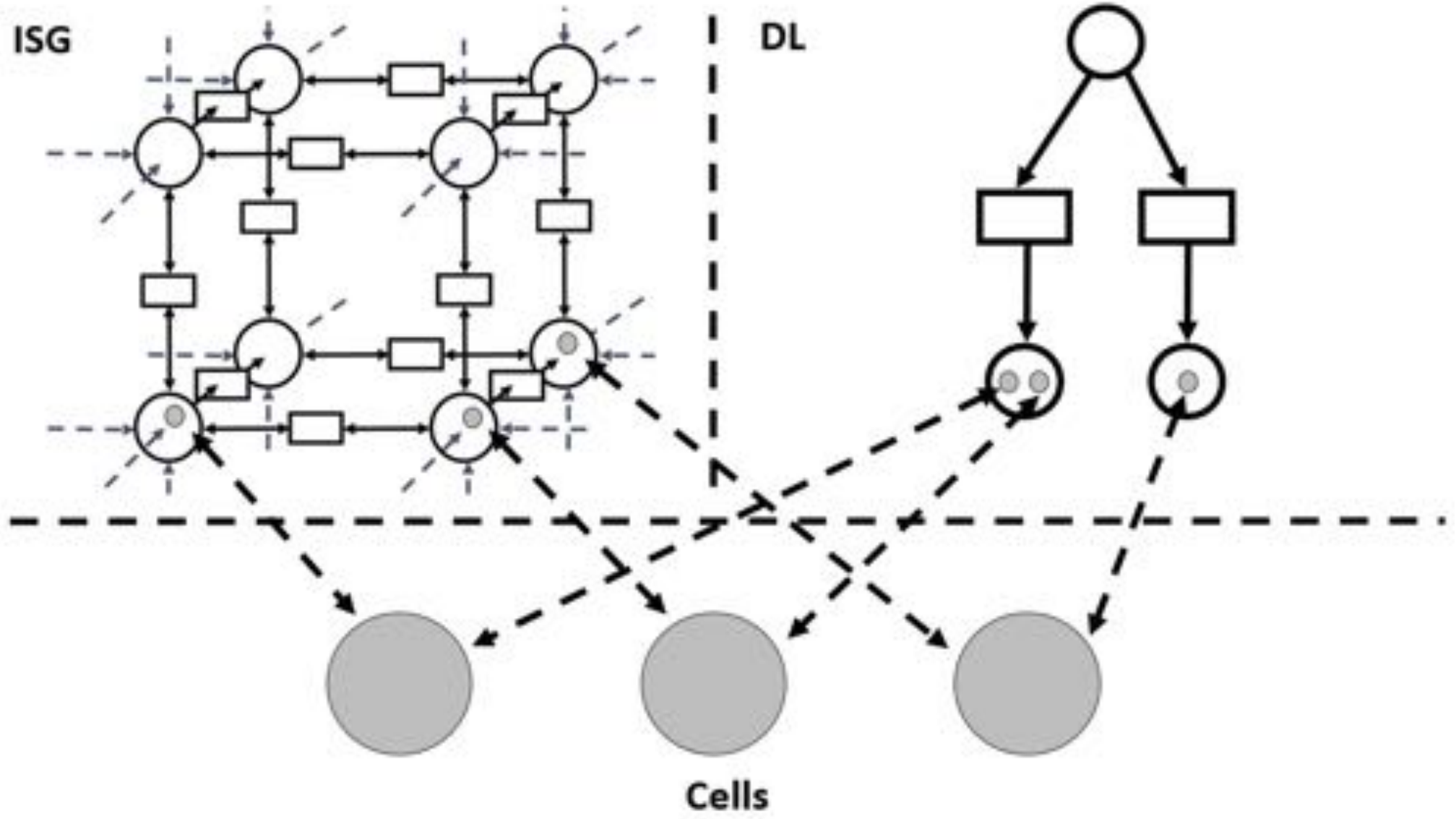
**Abstract** Synthetic Biology is characterized by a forward engineering approach to the design of biological systems implementing desired functionalities. The Synthetic Biology design cycle benefits from the understanding and the proper representation



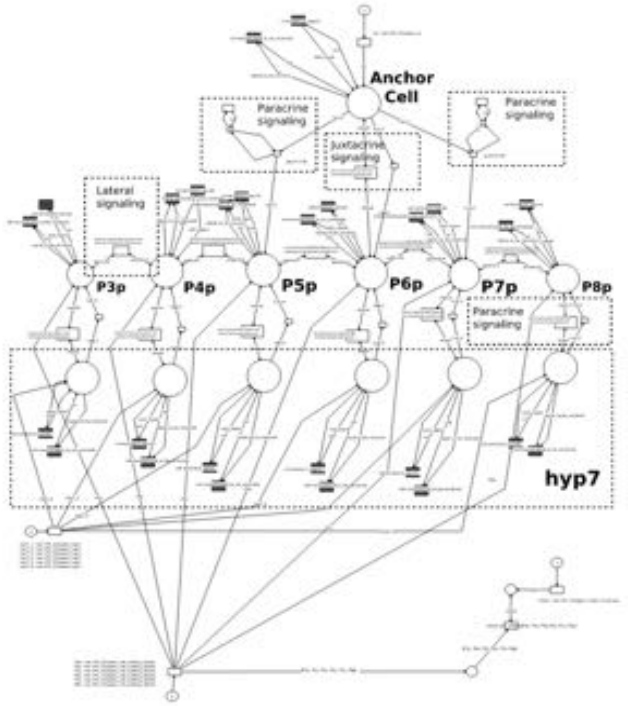


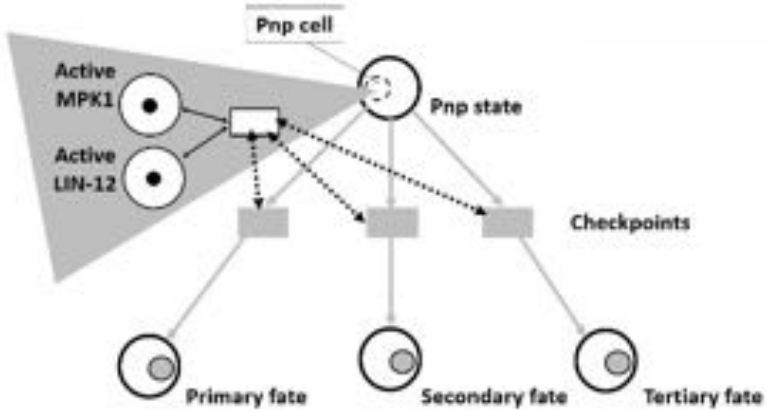


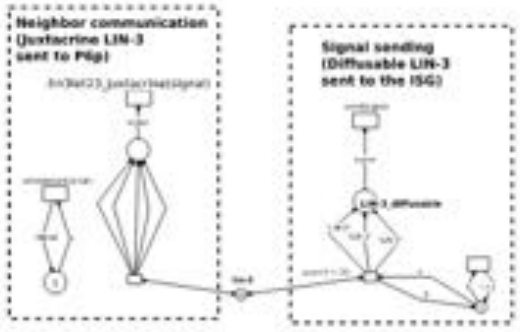
# F.A.I.R. enough?

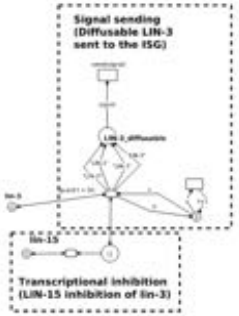


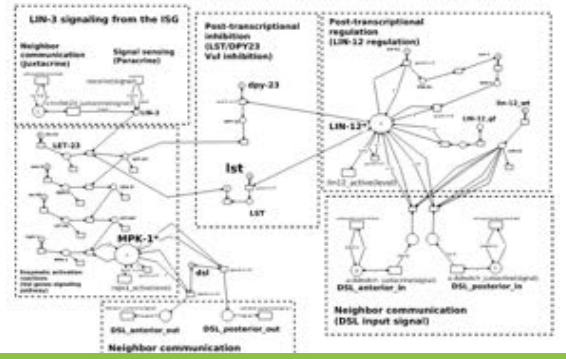

The modeling approach...



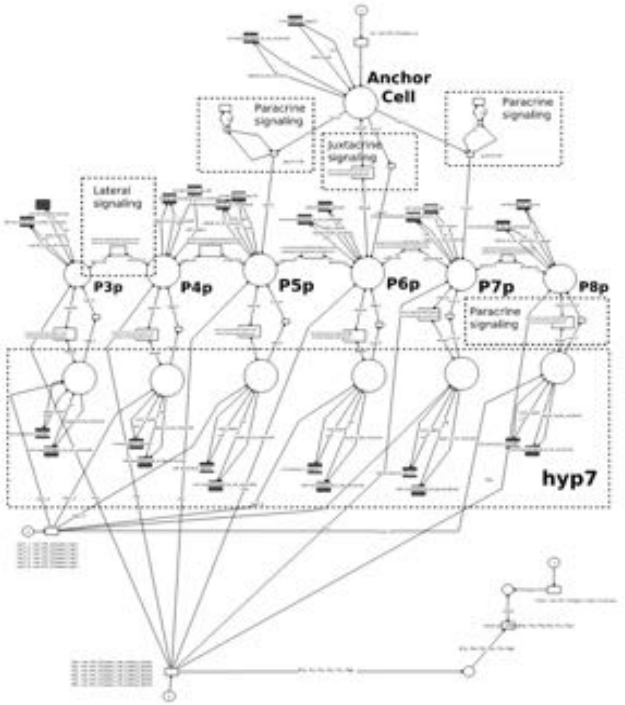



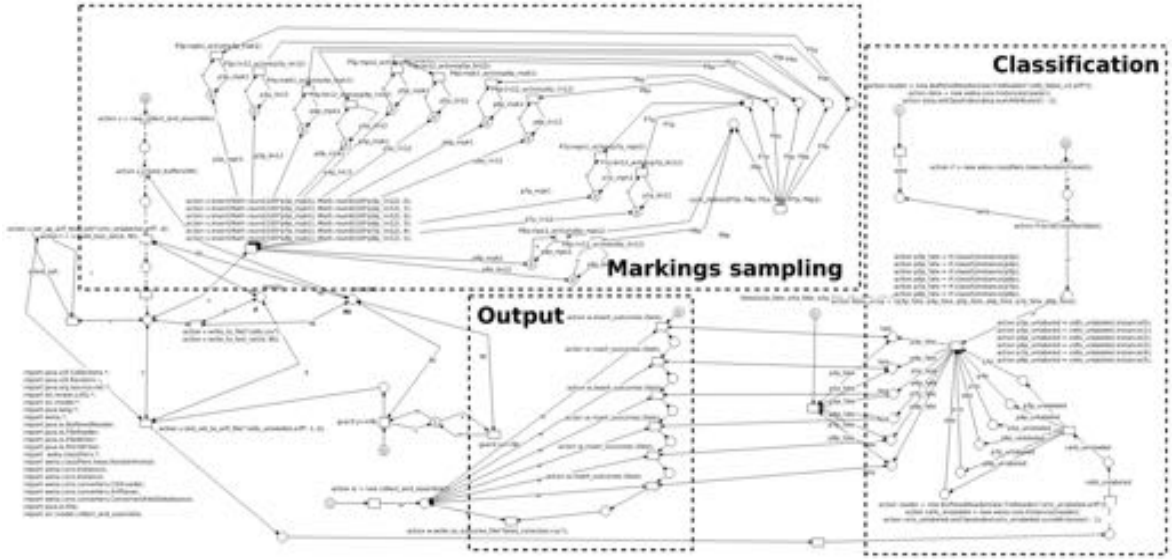



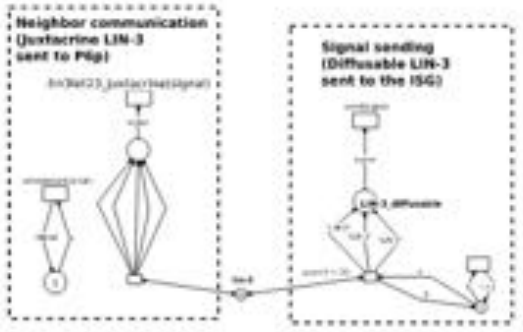



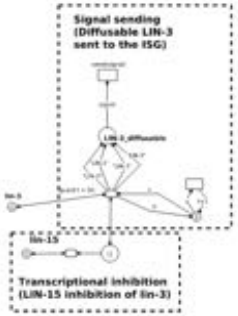

...but VPC specification looks more like this

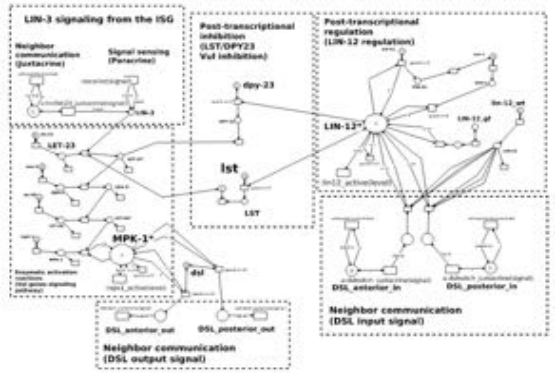
# ...or like this

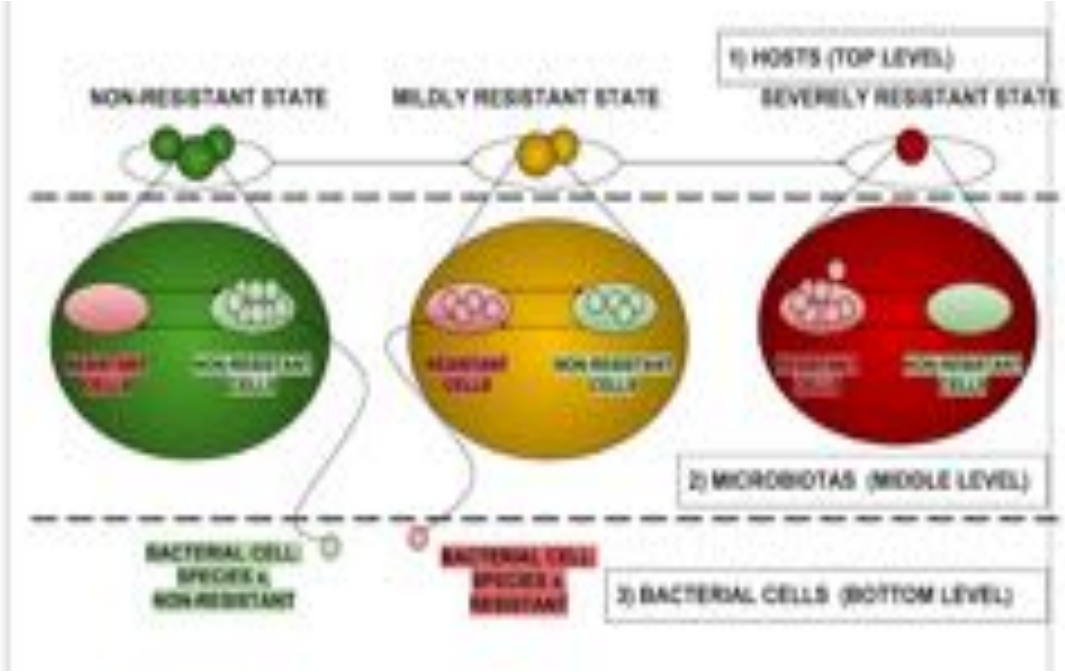

Anchor Cell
Paracrine signaling
Juxtacrine signaling
Paracrine signaling
Lateral signaling
P3p
P4p
P5p
P6p
P7p
P8p
Paracrine signaling
hyp7


Classification
Markings sampling
Output

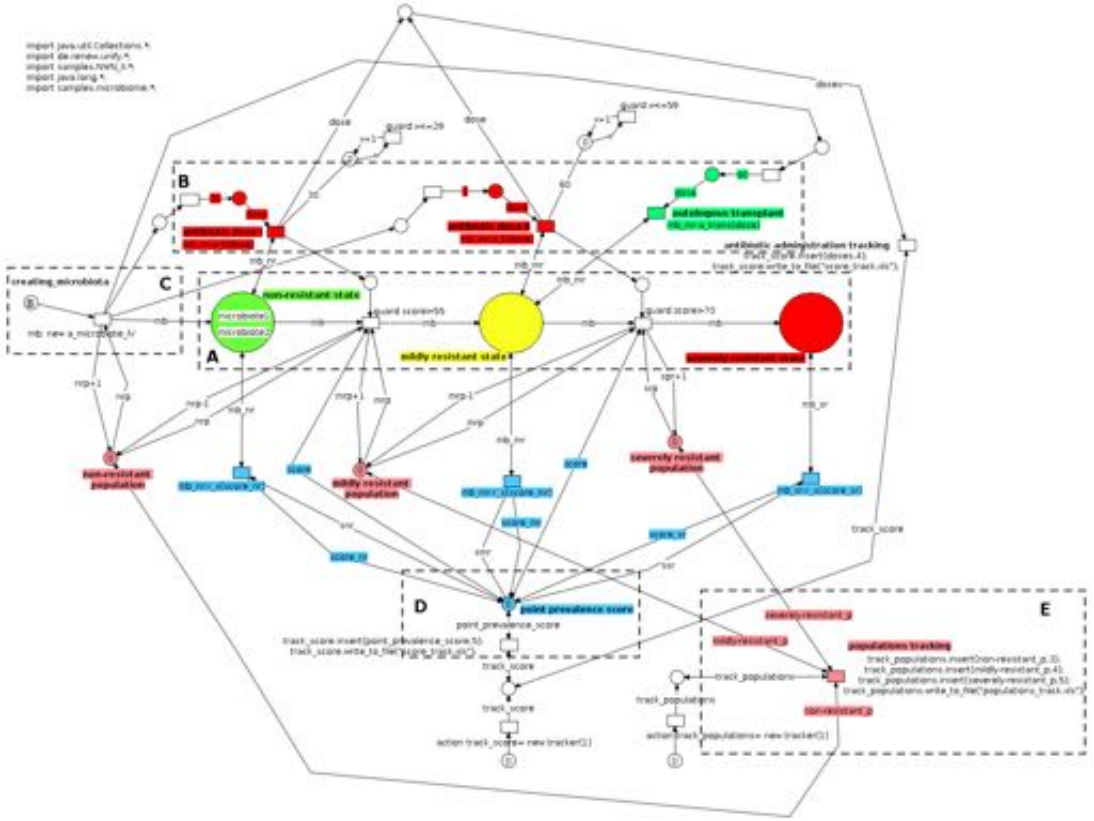

Neighbor communication (juxtacrine LIN-3 sent to P6p)
Signal sending (Diffusable LIN-3 sent to the ISG)

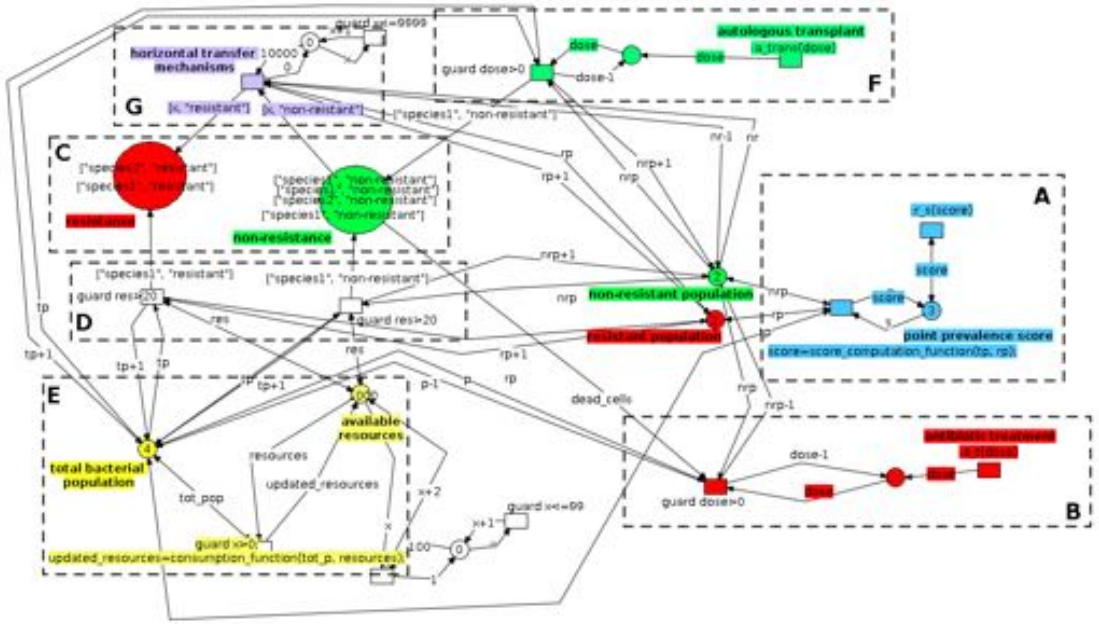

Signal sending (Diffusable LIN-3 sent to the ISG)
lin-15
Transcriptional inhibition (LIN-15 inhibition of lin-3)


LIN-3 signaling from the ISG
Neighbor communication (juxtacrine)
Signal sensing (Paracrine)
Post-transcriptional inhibition (LST/DPY23 Vul inhibition)
Post-transcriptional regulation (LIN-12 regulation)
dpy-23
LIN-12*
lst
LST
MPK-1*
dsl
DSL_anterior_in
DSL_posterior_in
DSL_anterior_out
DSL_posterior_out
Neighbor communication (DSL output signal)
Neighbor communication (DSL input signal)

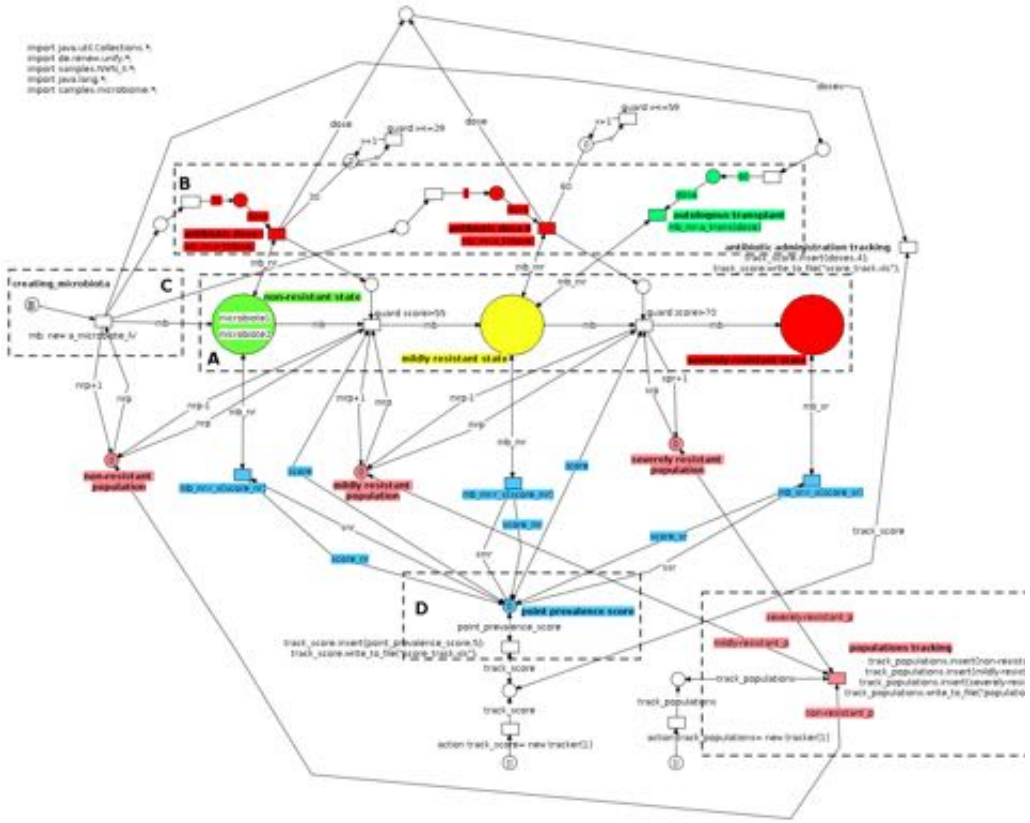


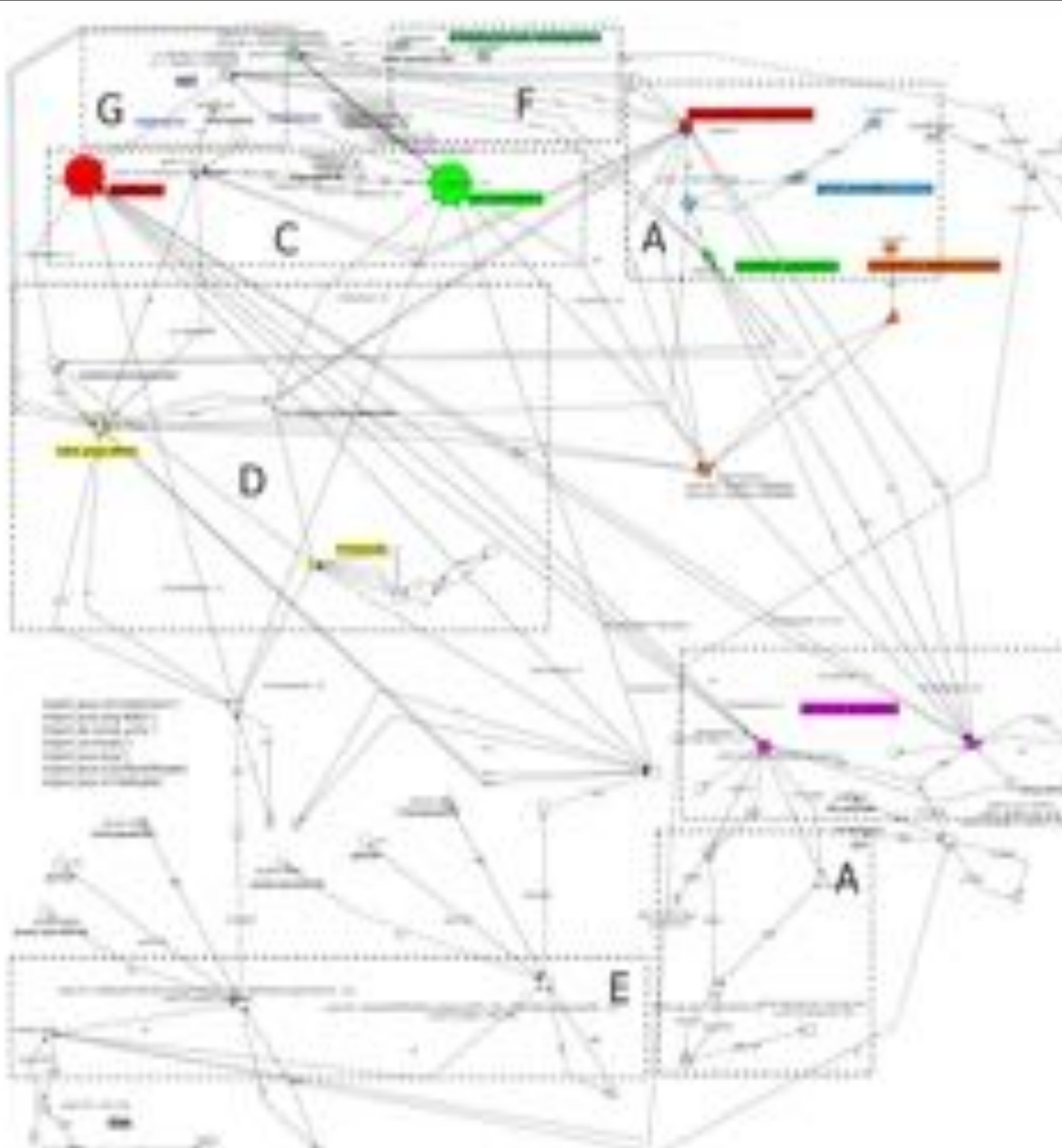

Abstraction makes things look simpler...

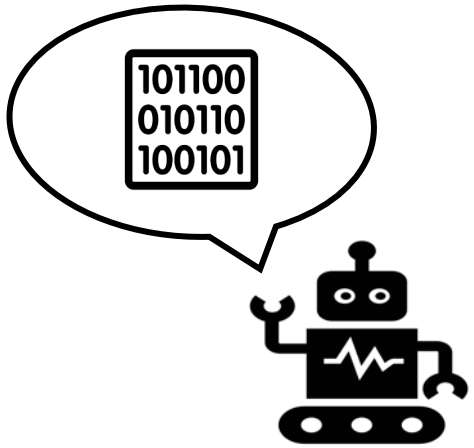


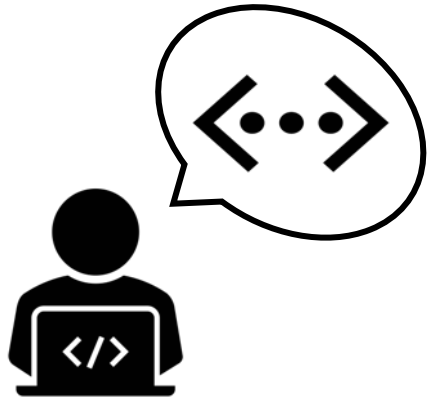


...than they look like in practice...


B
C
A
D
non-resistant state
mildly resistant state
non-resistant population
mildly resistant population
severely resistant population
point prevalence score
track_score
track_populations
populations tracking
autologous transplant
antibiotic administration tracking


G
F
C
A
D
A
E



## Findable

- For humans
- For machines

## Accessible

- Standardised communiction protocols
- Available metadata

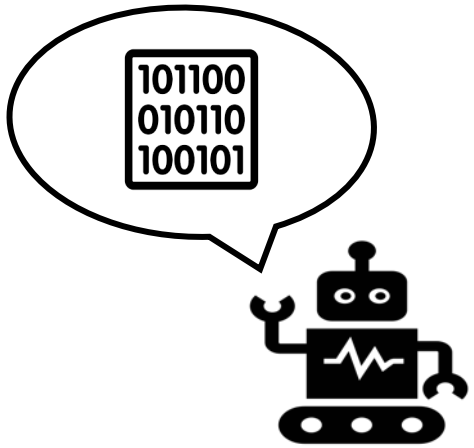
## Interoperable

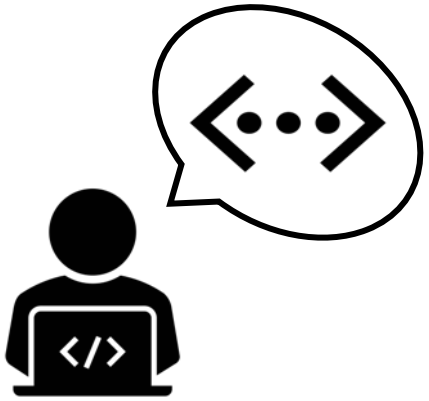
- Formal, accessible and shared language
- Qualified references to other (meta)data

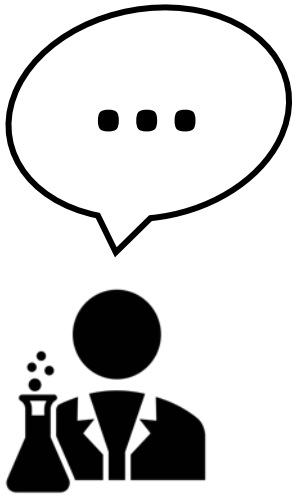
## Reusable

- Rich and relevant descriptions
- Domain-relevant community standards

**Is the modeling approach alone F.A.I.R. enough?**





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## Interoperable

- Formal, accessible and shared language
- Qualified references to other (meta)data

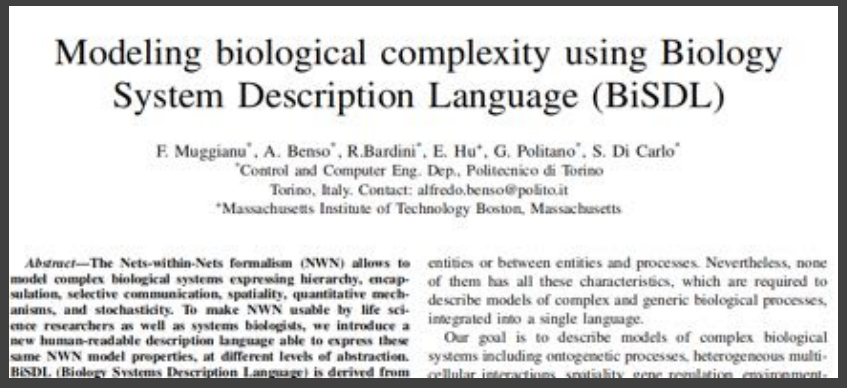
## Reusable

- Rich and relevant descriptions
- Domain-relevant community standards

**The framework needs to be relevant for the entire community**

# Biology System Description Language

# BiSDL generic template



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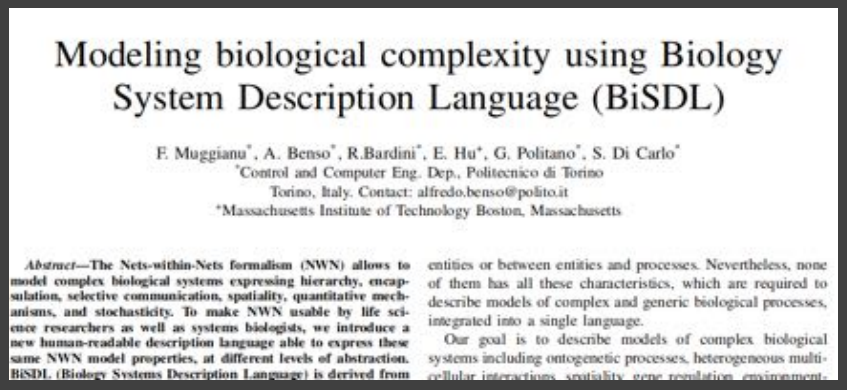
entities or between entities and processes. Nevertheless, none of them has all these characteristics, which are required to describe models of complex and generic biological processes, integrated into a single language.

Our goal is to describe models of complex biological systems including ontogenetic processes, heterogeneous multi-cellular interactions, spatiality, gene regulation, environment,

```
PACKAGE <package1>
...
PACKAGE <packageN>

ONTOLOGY <ONTOLOGY_NAME>=<url>
...
ONTOLOGY <ONTOLOGY_NAME>=<url>

MODULE <name> (<type> <nameparam>,.....)

 BIOLOGICAL REFERENCE
   <ONTOLOGY_NAME>.<ID_WITHIN_THE_ONTOLOGY>

 ENTITIES
   PLACE <name_place>,....
   ENTITY <name_entity>,....
   CHANNEL <name_channel>,....

 INIT
   <place_name>.attribute(<value>)
   <entity_name>.attribute(<value>)
   <entity_name> = <module_entity_name>(<params>,..)

 PROCESSES
   process(  keywordrentities_declaration,
       keywordrentities_declaration,
       ...,
       (transition_function),
       delay(N)
   )

   <module_process_name>(<param>,....)
END
```

High-level BiSDL model descriptions follow a generic template

# BiSDL generic template



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```
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...
PACKAGE <packageN>

ONTOLOGY <ONTOLOGY_NAME>=<url>
...
ONTOLOGY <ONTOLOGY_NAME>=<url>

MODULE <name> (<type> <nameparam>,.....)

 BIOLOGICAL REFERENCE
   <ONTOLOGY_NAME>:<ID_WITHIN_THE_ONTOLOGY>

 ENTITIES
   PLACE <name_place>,....
   ENTITY <name_entity>,....
   CHANNEL <name_channel>,....

 INIT
   <place_name>.attribute(<value>)
   <entity_name>.attribute(<value>)
   <entity_name> = <module_entity_name>(<params>,..)

 PROCESSES
   process(  keywordrentities_declaration,
       keywordrentities_declaration,
       ...,
       (transition_function),
       delay(N)
   )

   <module_process_name>(<param>,....)
END
```


**Structural** descriptions cover functional modules

**Behavioral** descriptions cover their functional relationships

# BiSDL descriptions

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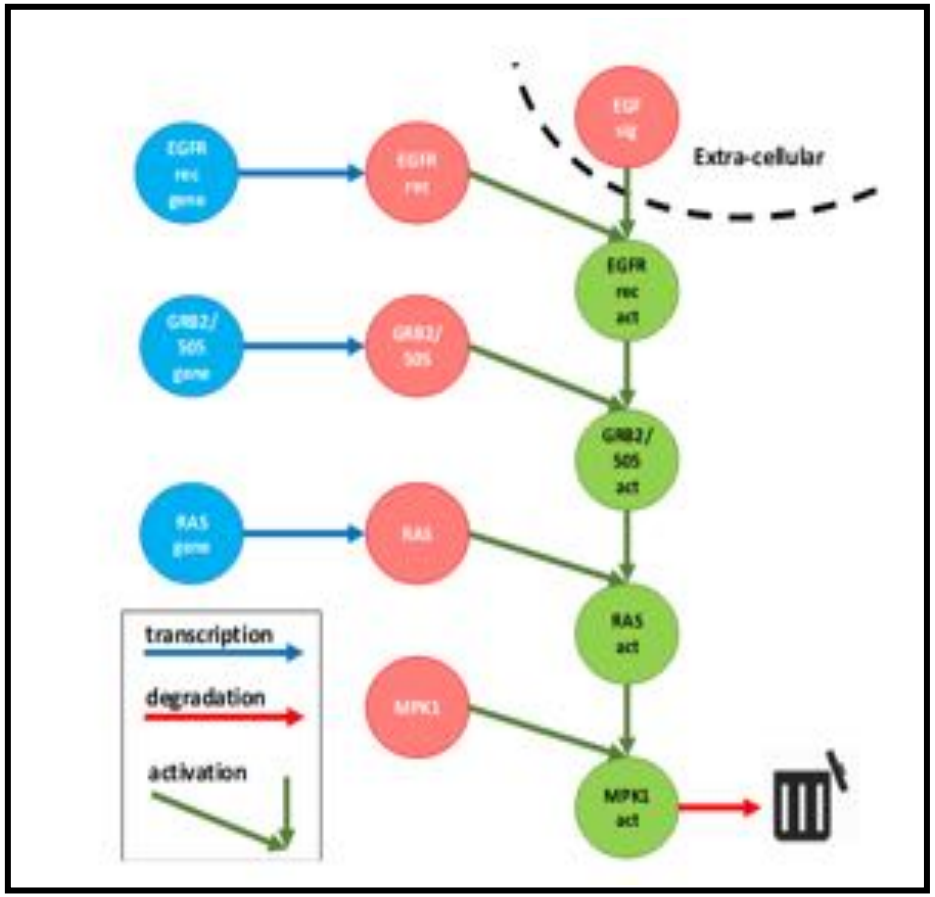
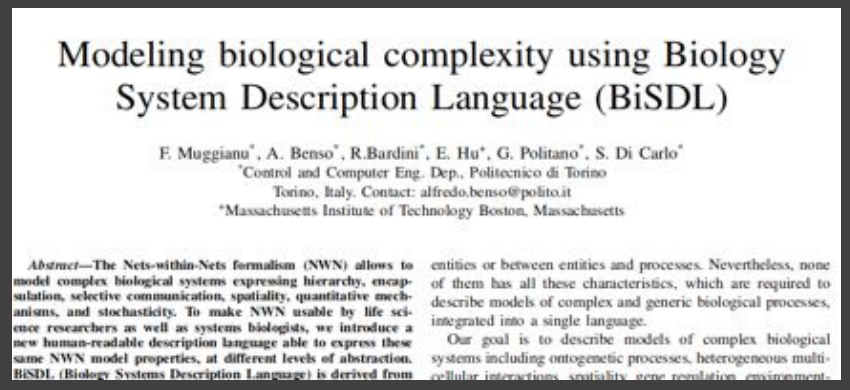


# BiSDL descriptions



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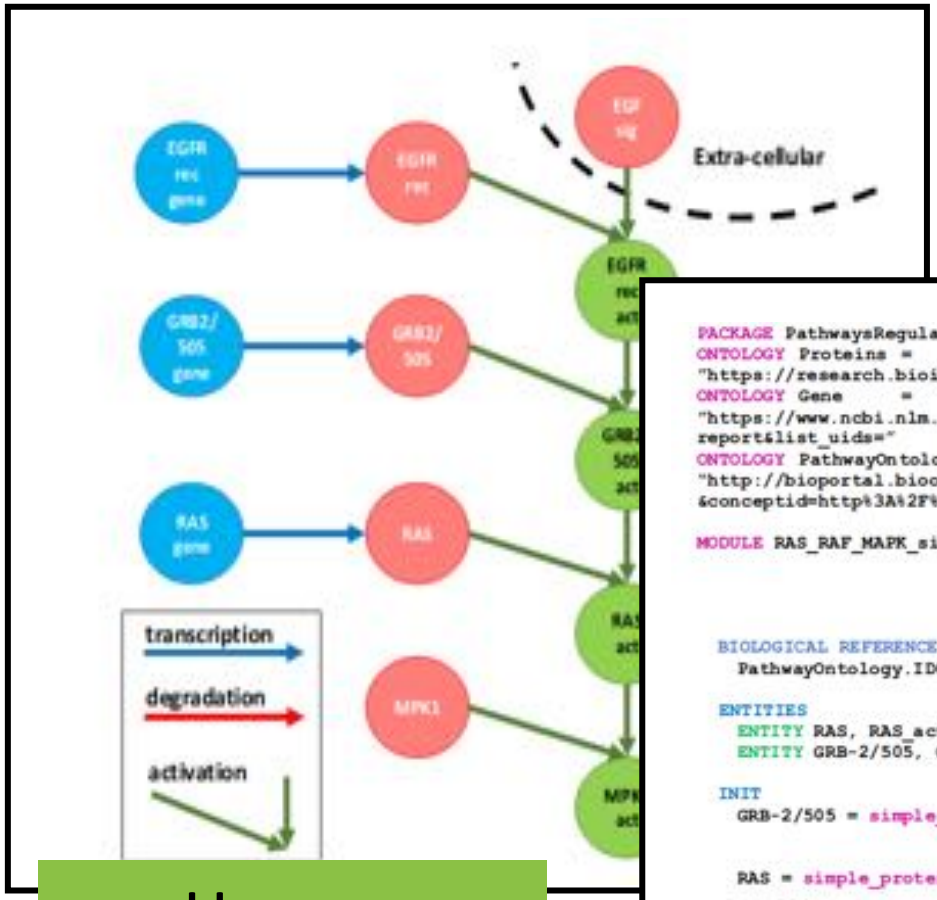


```
PACKAGE PathwaysRegulations
ONTOLOGY Proteins =
"https://research.bioinformatics.udel.edu/pro/entry/PR%3A"
ONTOLOGY Gene     =
"https://www.ncbi.nlm.nih.gov/gene?cmd=Retrieve&dopt=full_
report&list_uids="
ONTOLOGY PathwayOntology    =
"http://bioportal.bioontology.org/ontologies/PTS/?p=classes
&conceptid=http%3A%2F%2Fscai.fraunhofer.de%2FFWDICT%23"

MODULE RAS_RAF_MAPK_sig_path (ENTITY EGF-like_signal,
                              ENTITY mpk_1_act,
                              ENTITY mpk_1,
                              ENTITY EGFR-likeRec)

  BIOLOGICAL REFERENCE
    PathwayOntology.ID0176

  ENTITIES
    ENTITY RAS, RAS_act, EGFR-likeRec_act
    ENTITY GRB-2/505, GRB-2/505_act

  INIT
    GRB-2/505 = simple_protein("GRB2/505",
                               Proteins.000008220,
                               black_token()*3)
    RAS = simple_protein("RAS",Proteins.000013743,
                         black_token()*3)
    GRB-2/505_act = simple_protein("GRB-2/505_act",
                    Proteins.000008220,black_token()*3)
    RAS_act = simple_protein("RAS_act",
                  Proteins.000013743,black_token()*3)
    EGFR-likeRec_act = simple_protein("EGFR-likeRec_act",
                  Proteins.000006933,black_token()*3)

  PROCESSES
    transcription(RAS, Gene.3845)
    transcription(EGFR-likeRec, Gene.1956)
    transcription(GRB-2/505, Gene.2885)
    activation(EGFR-likeRec, EGF-like_signal,
               EGFR-likeRec_act)
    activation(GRB-2/505, EGFR-likeRec_act,
               GRB-2/505_act )
    activation(RAS, GRB-2/505_act, RAS_act)
    activation(mpk_1, RAS_act, mpk_1_act)
    degradation(mpk_1_act, 100)
END
```

Human readability

Machine-readiness

# BiSDL descriptions

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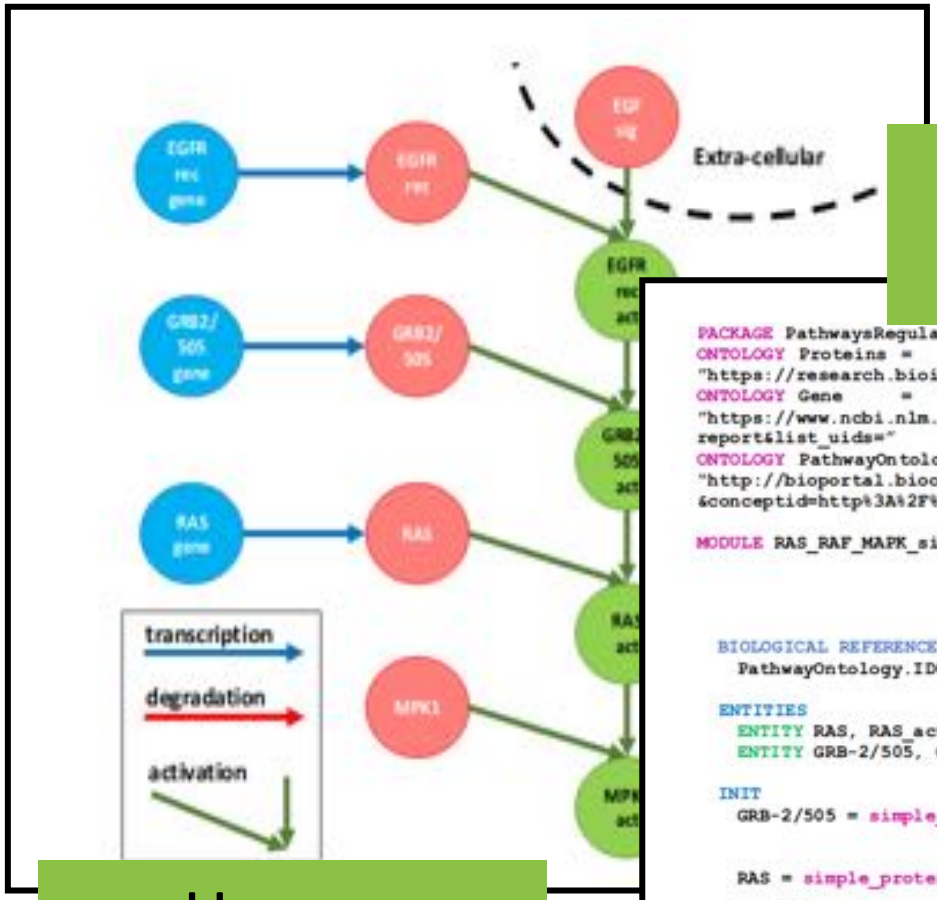


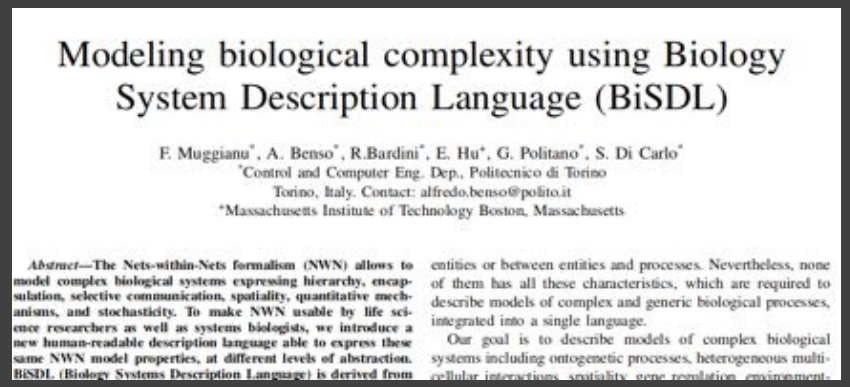

Findable references

Human readability

Machine-readiness

```
PACKAGE PathwaysRegulations
ONTOLOGY Proteins =
"https://research.bioinformatics.udel.edu/pro/entry/PR%3A"
ONTOLOGY Gene     =
"https://www.ncbi.nlm.nih.gov/gene?cmd=Retrieve&dopt=full_
report&list_uids="
ONTOLOGY PathwayOntology    =
"http://bioportal.bioontology.org/ontologies/PTS/?p=classes
&conceptid=http%3A%2F%2Fscai.fraunhofer.de%2FFWDICT%23"

MODULE RAS_RAF_MAPK_sig_path (ENTITY EGF-like_signal,
                              ENTITY mpk_1_act,
                              ENTITY mpk_1,
                              ENTITY EGFR-likeRec)

  BIOLOGICAL REFERENCE
    PathwayOntology.ID0176

  ENTITIES
    ENTITY RAS, RAS_act, EGFR-likeRec_act
    ENTITY GRB-2/505, GRB-2/505_act

  INIT
    GRB-2/505 = simple_protein("GRB2/505",
                               Proteins.000008220,
                               black_token()*3)
    RAS = simple_protein("RAS",Proteins.000013743,
                         black_token()*3)
    GRB-2/505_act = simple_protein("GRB-2/505_act",
                    Proteins.000008220,black_token()*3)
    RAS_act = simple_protein("RAS_act",
                  Proteins.000013743,black_token()*3)
    EGFR-likeRec_act = simple_protein("EGFR-likeRec_act",
                  Proteins.000006933,black_token()*3)

  PROCESSES
    transcription(RAS, Gene.3845)
    transcription(EGFR-likeRec, Gene.1956)
    transcription(GRB-2/505, Gene.2885)
    activation(EGFR-likeRec, EGF-like_signal,
               EGFR-likeRec_act)
    activation(GRB-2/505, EGFR-likeRec_act,
               GRB-2/505_act )
    activation(RAS, GRB-2/505_act, RAS_act)
    activation(mpk_1, RAS_act, mpk_1_act)
    degradation(mpk_1_act, 100)
END
```

# BiSDL descriptions



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Modules to be shared in **libraries**

```
MODULE simple_gene (STRING name, TOKEN token, STRING ID)
  BIOLOGICAL REFERENCE
    ID
  ENTITIES
    PLACE gene
  INIT
    gene.name = name
    gene.token( token )
END

MODULE transcription (ENTITY protein, STRING ID)
  ENTITIES
    PLACE gene
  INIT
    gene = simple gene(protein.name + "_wt",ID,
                       black_token())
  PROCESSES
    process(BI:{gene}, OUT:{protein} )
END

MODULE degradation (ENTITY protein, INT n)
  PROCESSES
    process(IN:{protein}, delay(n) )
END
```

Human readability

Machine-readiness

Findable references

```
GE PathwaysRegulations
OGY Proteins =
s://research.bioinformatics.udel.edu/pro/entry/PR%3A"
OGY Gene     =
s://www.ncbi.nlm.nih.gov/gene?cmd=Retrieve&dopt=full_
t&list_uids="
OGY PathwayOntology    =
://bioportal.bioontology.org/ontologies/PTS/?p=classes
eptid=http%3A%2F%2Fscai.fraunhofer.de%2FFWDICT%23"

E RAS_RAF_MAPK_sig_path (ENTITY EGF-like_signal,
                         ENTITY mpk_1_act,
                         ENTITY mpk_1,
                         ENTITY EGFR-likeRec)

LOGICAL REFERENCE
athwayOntology.ID0176

ITIES
NTITY RAS, RAS_act, EGFR-likeRec_act
NTITY GRB-2/505, GRB-2/505_act

RB-2/505 = simple_protein("GRB2/505",
                          Proteins.000008220,
                          black_token()*3)
AS = simple_protein("RAS",Proteins.000013743,
                    black_token()*3)
RB-2/505_act = simple_protein("GRB-2/505_act",
                    Proteins.000008220,black_token()*3)
AS_act = simple_protein("RAS_act",
                    Proteins.000013743,black_token()*3)
GFR-likeRec_act = simple_protein("EGFR-likeRec_act",
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CESSES
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transcription(EGFR-likeRec, Gene.1956)
transcription(GRB-2/505, Gene.2885)
activation(EGFR-likeRec, EGF-like_signal,
           EGFR-likeRec_act)
activation(GRB-2/505, EGFR-likeRec_act,
           GRB-2/505_act )
activation(RAS, GRB-2/505_act, RAS_act)
activation(mpk_1, RAS_act, mpk_1_act)
degradation(mpk_1_act, 100)
END
```
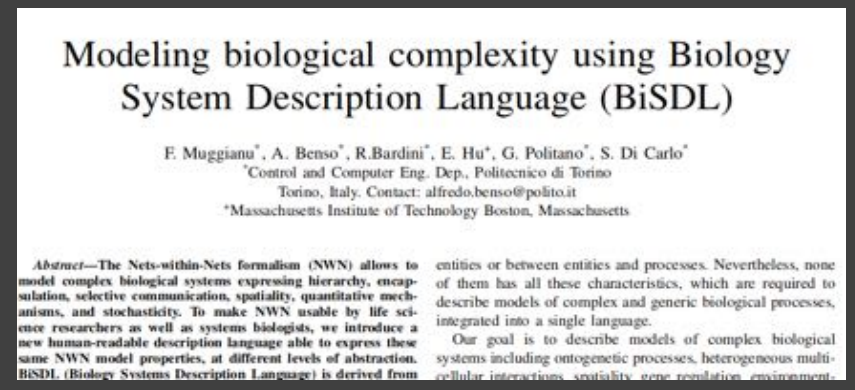

# Flow

From high-level BiSDL descriptions to NWNs models and simulations



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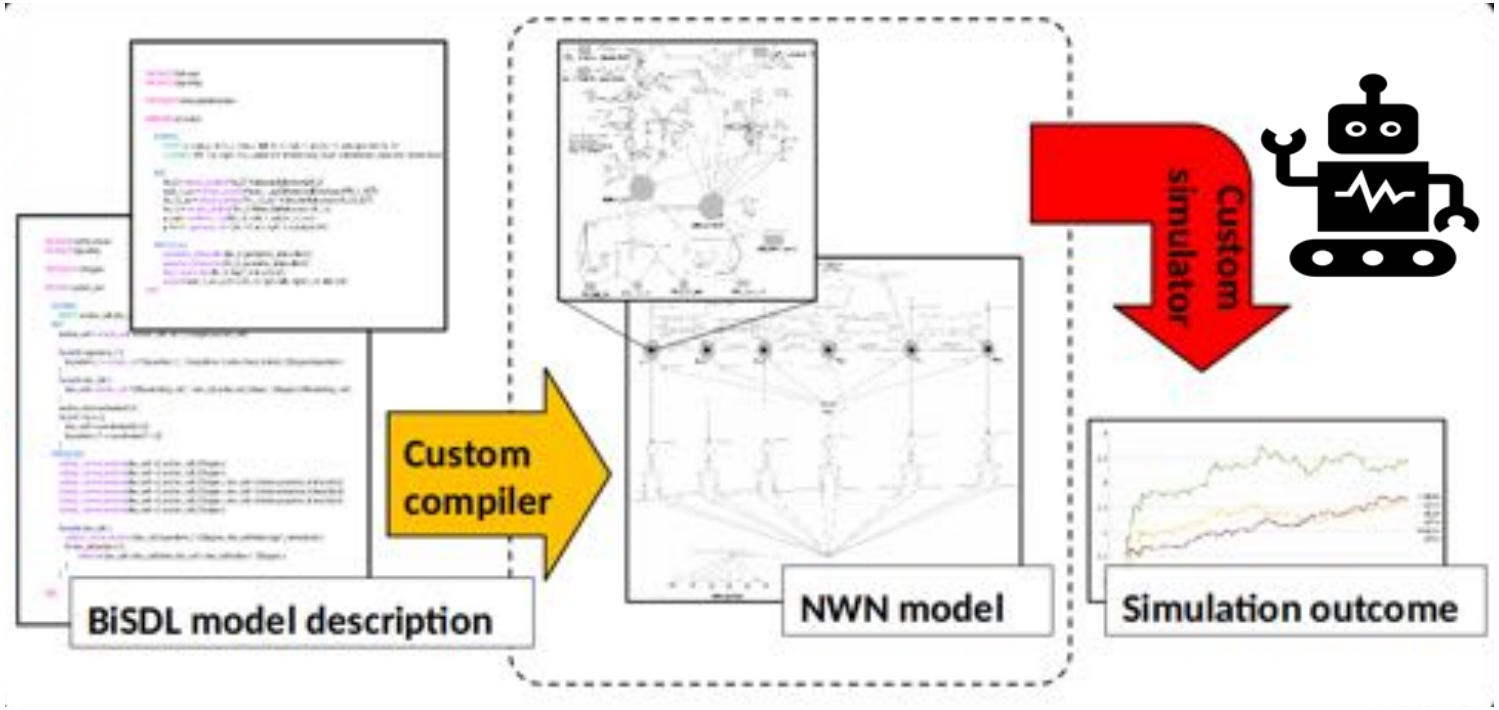

# Flow

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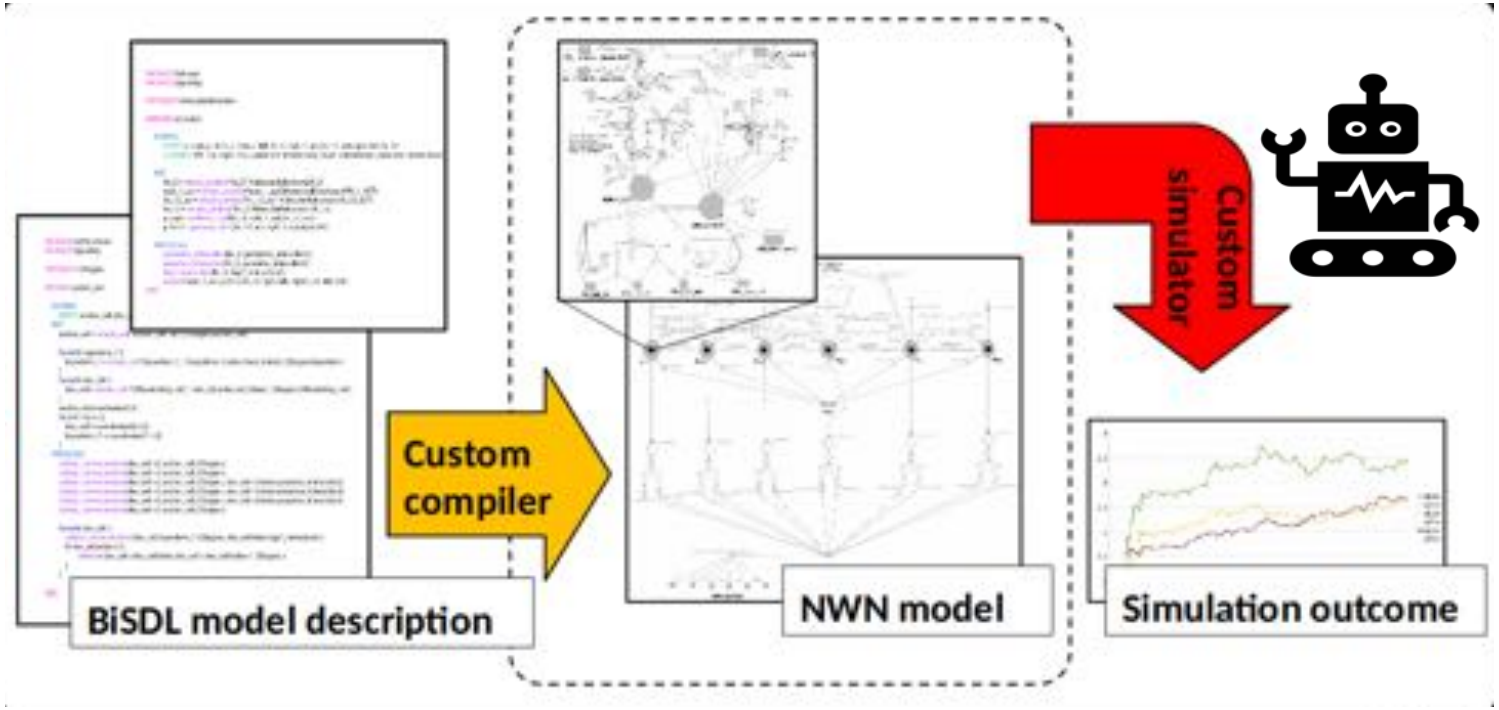


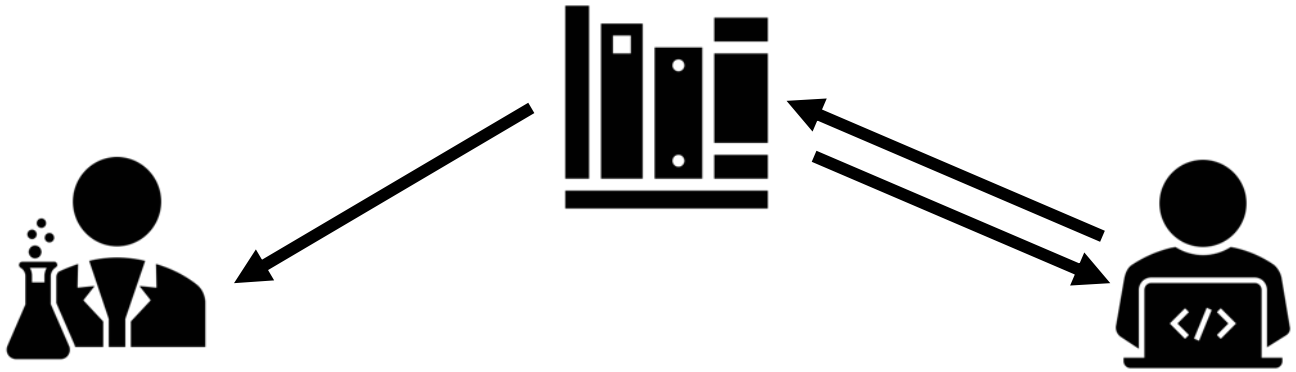

Computational biologists encode knowledge into modules, experimental biologists reuse them.

# 6. Future perspectives

# Necessary improvements

| | |
|---|---|
| **Modeling approach** | Hybrid simulations of molecular diffusion |
| | Automated and **data-driven model construction** |
| Flow usability | BiSDL visual language |
| | Populate BiSDL libraries |
| | Test with **diverse user** base |
| **Industrial applications** | Knowledge management and automation for biotech and pharma industries |

# First steps

| | |
|---|---|
| **Modeling approach** | Efficient simulation of morphogen gradient formation |
| | scRNA-seq data analysis of cerebellar astrocytes heterogeneity in development |
| **Flow usability** | Bioinformatic pipelines for biologists to characterize nutraceutical agrifood products |
| **Industrial applications** | Computational method to improve cell culture processes - ***patent pending*** |

1. Bardini, Roberta; Benso, Alfredo; Di Carlo, Stefano; Politano, Gianfranco; Savino, Alessandro; **Using nets-within-nets for modeling differentiating cells in the epigenetic landscape**, International Conference on Bioinformatics and Biomedical Engineering, 315-321, 2016, Springer
2. Bardini, Roberta; Di Carlo, Stefano; Politano, Gianfranco; Benso, Alfredo; **Modeling antibiotic resistance in the microbiota using multi-level Petri Nets**, BMC systems biology, 12, 6, 108, 2018, BioMed Central
3. Bardini, Roberta; Politano, Gianfranco; Benso, Alfredo; Di Carlo, Stefano; **Computational Tools for Applying Multi-level Models to Synthetic Biology**, Synthetic Biology, 95-112, 2018, Springer
4. Muggianu, F; Benso, Alfredo; Bardini, Roberta; Hu, E; Politano, Gianfranco; Di Carlo, Stefano; **Modeling biological complexity using Biology System Description Language (BiSDL)**, 2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM), 713-717, 2018, IEEE
5. Bardini, Roberta; Politano, Gianfranco; Benso, Alfredo; Di Carlo, Stefano; **Using multi-level petri nets models to simulate microbiota resistance to antibiotics**, 2017 IEEE International Conference on Bioinformatics and Biomedicine (BIBM), 128-133, 2017, IEEE
6. Bardini, R; Politano, G; Benso, A; Di Carlo, S; **Multi-level and hybrid modelling approaches for systems biology**, Computational and structural biotechnology journal, 15, 396-402, 2017, Elsevier
7. Distasi, Carla; Dionisi, Marianna; Ruffinatti, Federico Alessandro; Gilardino, Alessandra; Bardini, Roberta; Antoniotti, Susanna; Catalano, Federico; Bassino, Eleonora; Munaron, Luca; Martra, Gianmario; **The interaction of SiO2 nanoparticles with the neuronal cell membrane: activation of ionic channels and calcium influx**, Nanomedicine, 14, 5, 575-594, 2019, Future Medicine

- Journal paper extension of **Modeling biological complexity using Biology System Description Language (BiSDL)** conference paper (to be submitted in 2019)
- Journal paper centered on the **modeling approach and VPC specification example** (to be submitted in 2019)

# Thank you