From viruses to cells: Membrane systems modelling pandemics

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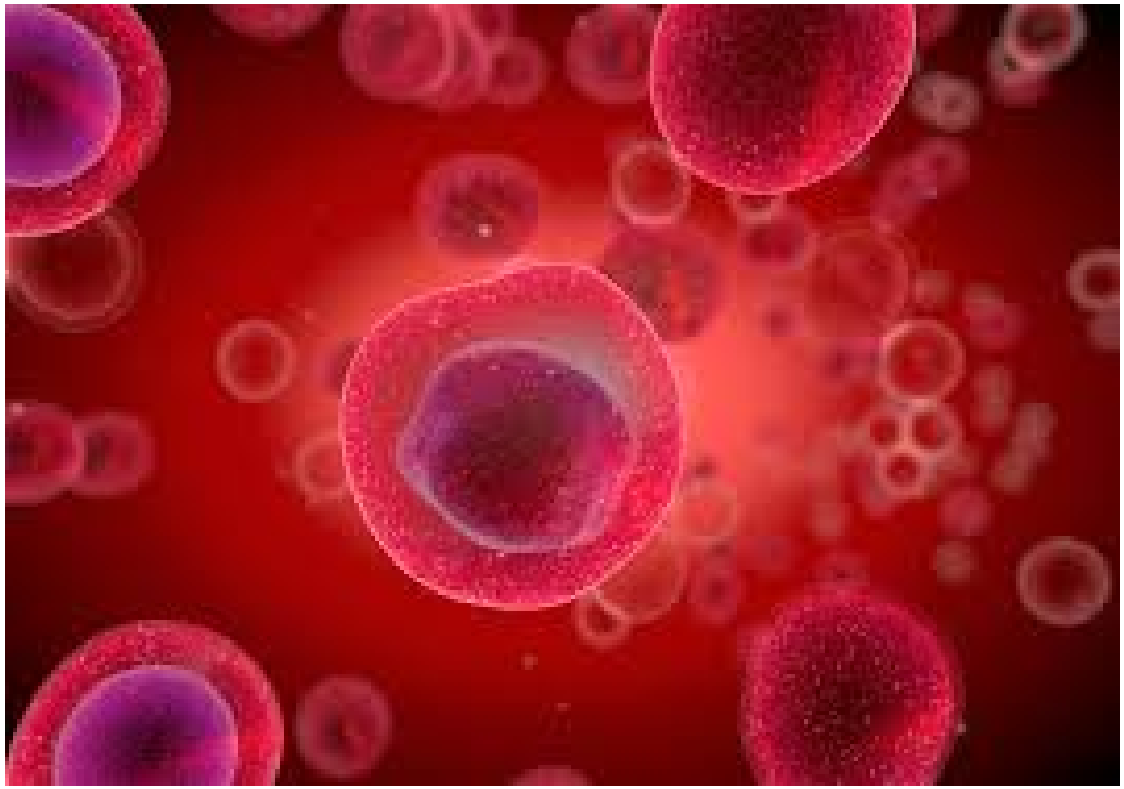
LIFE !

Principles of Life

* Replication of genetic material.
* Protein synthesis.
* Energy manufacture.
* Implementation of metabolic processes.

Cells

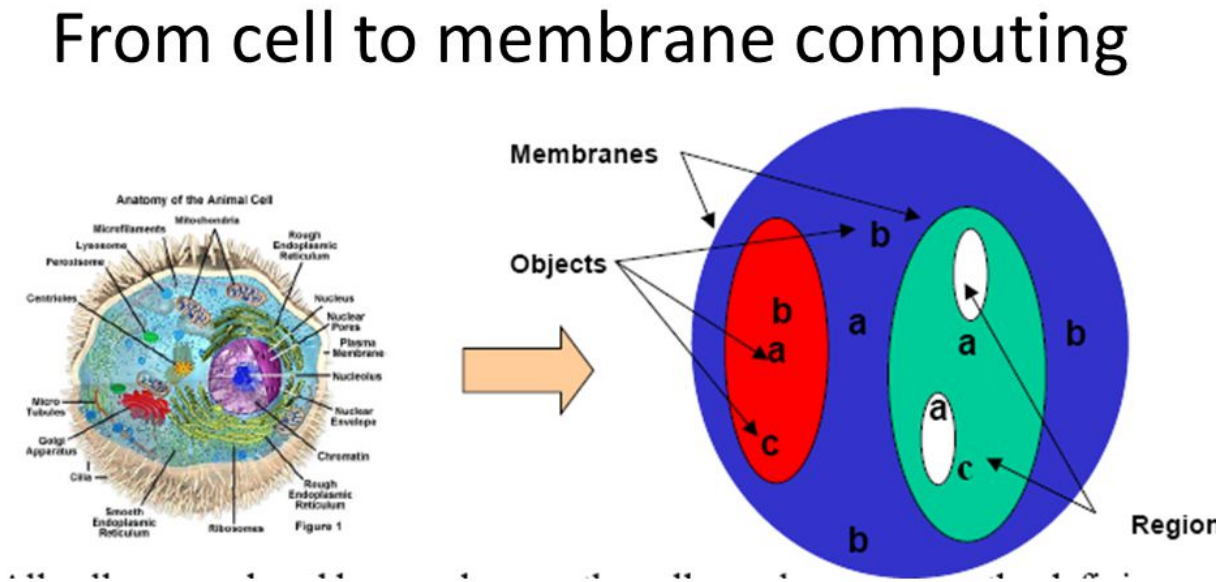


The **basic unit** of **life**.

They have a complex hierarchical structure (**biological membranes**).

Membrane Computing

In 1998[1], Gh. Păun introduced a new computing paradigm inspired by the **architecture** and the **functioning** of **living cells**.



All cells are enclosed by membranes; the cell membrane acts as the defining principle of what constitutes a cell and the rest of the world. Cells need to be able to transport proteins, DNA, and ions across the membrane.

[1] Gh. Păun. Computing with membranes. **Journal of Computer and System Sciences**, **61**, 1 (2000), 108–143, and Turku Center for CS-TUCS Report No. 208, 1998.

Membrane Computing

This paradigm provides distributed, parallel non-deterministic computing models (computational devices: **membrane systems**).

Generally, membrane systems are equivalent in power to Turing machines[1]

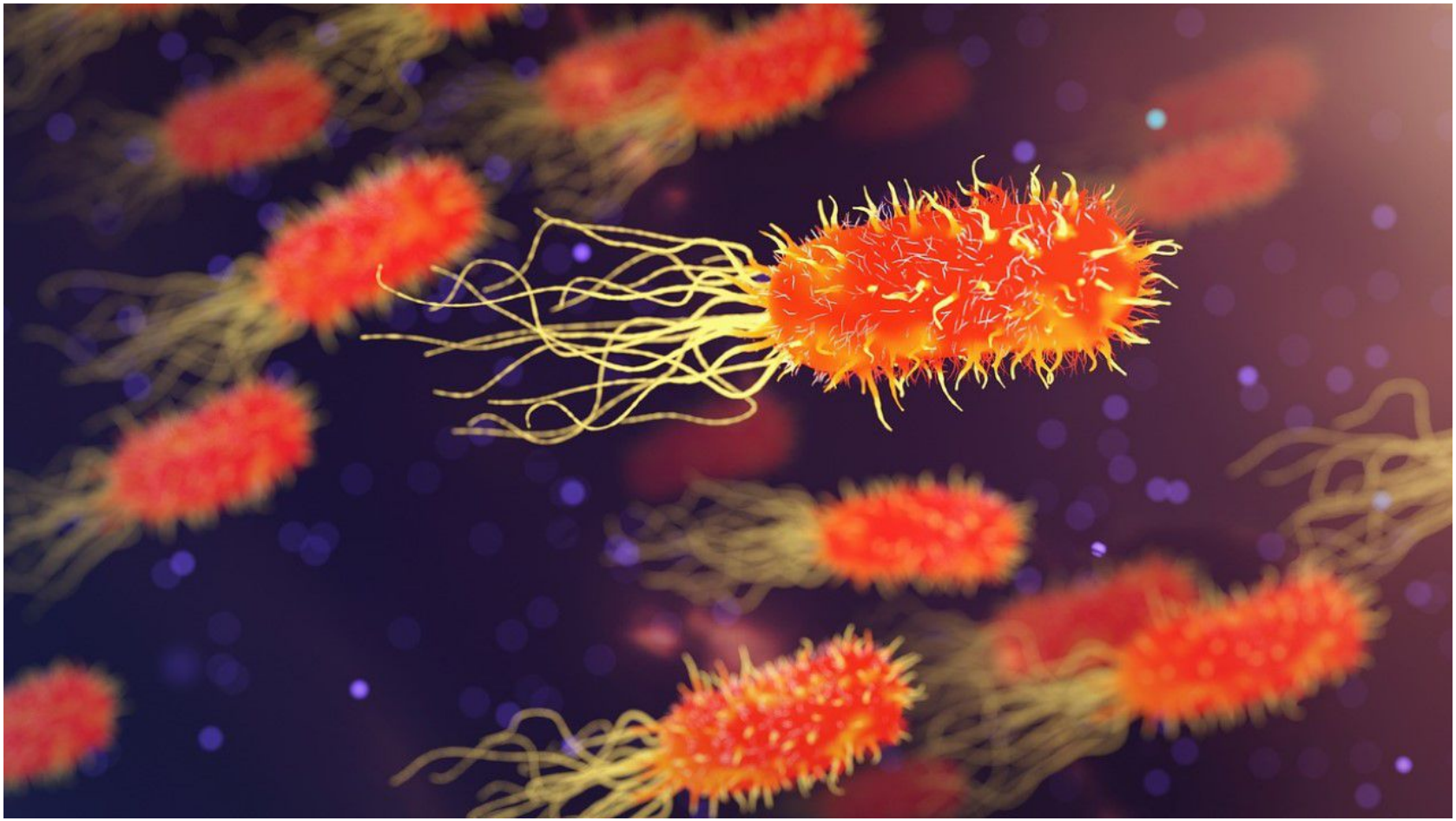
They have the ability to:

- ⋆ **Generate** all **diophantine sets**[2]
- ⋆ **Compute** all **recursive functions**[3]

[2] M.J. Pérez-Jiménez, A. Romero. Generation of Diophantine Sets by Computing P Systems with External Output. **Lecture Notes in Computer Science**, **2509** (2002), 176-190.

[3] M.J. Pérez-Jiménez, A. Romero. Computing partial recursive functions by transition P systems. **Lecture Notes in Computer Science**, **2933** (2004), 320-340.

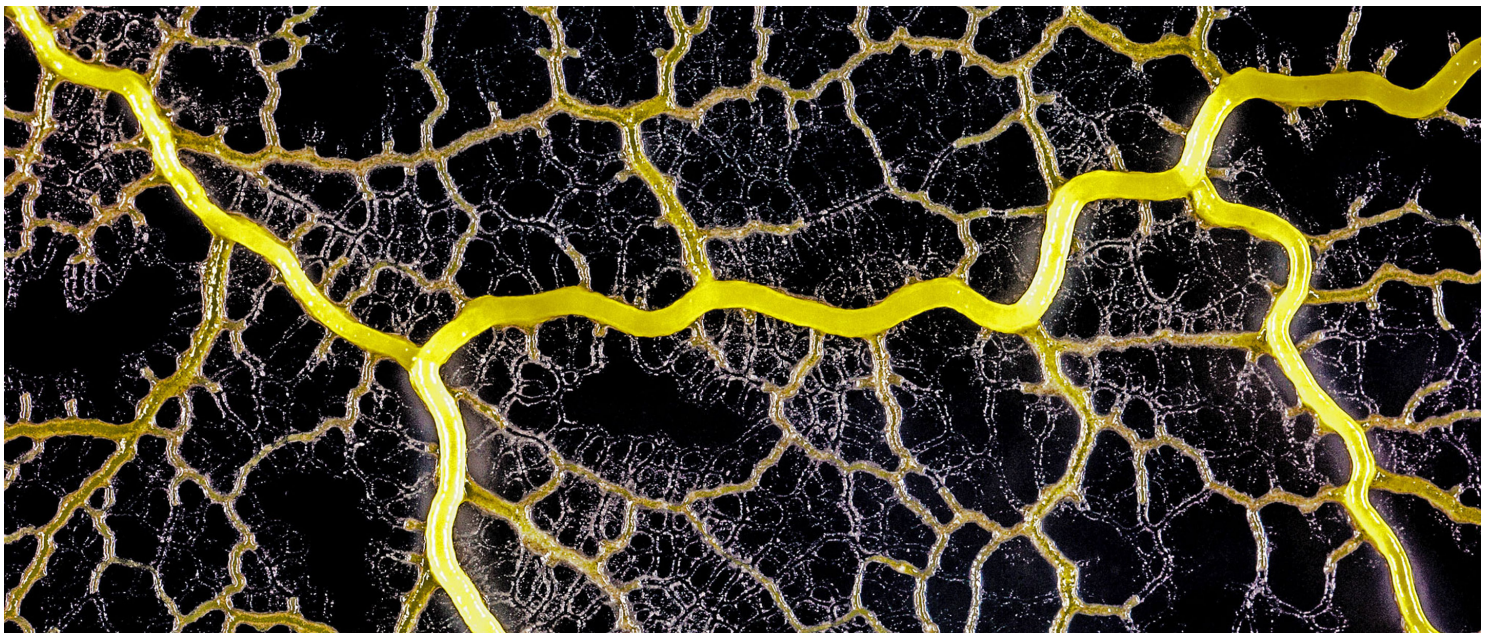
Bacteria



Bacteria are generally considered to be **independent unicellular organisms**.

Bacterial intelligence

Bacteria can take inputs (chemical signals), process them, producing output to signal other bacteria in the colony (they "walk" accross a surface).



The bacteria are not so different from smart robots programmed to respond to their environment

Intelligent communication of bacteria

Certain bacteria have a gene regulation system that allows an entire population of bacterial cells to communicate (the **quorum sensing** phenomenon).

* To regulate the **expression** of specific **genes** in a coordinated way depending on the **size of the population**.

It was first discovered by K. Nealson, T. Platt, and J. W. Hastings (in 1970)[4-5]

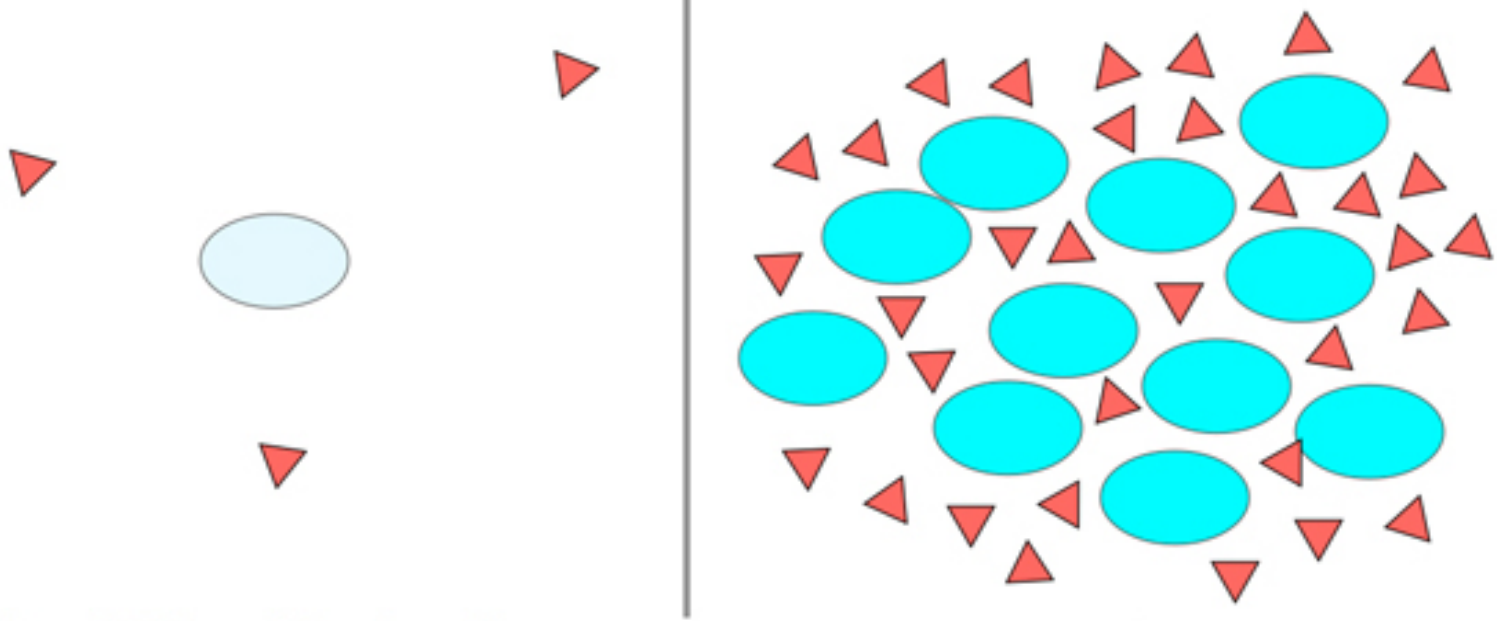
[4] K. Nealson, T. Platt, and J. Woodland Hastings: Cellular Control of the Synthesis and Activity of the Bacterial Luminescent System. **Journal of Bacteriology**, **104**, 1 (1970), 313-322.

[5] K.H. Nealson, J.W. Hastings. Bacterial bioluminescence: its control and ecological significance. *Microbiology Reviews*, **43**, 4 (1979), 496-518.

Bacterial Quorum Sensing

Low Cell Density

High Cell Density



Individual Behaviors

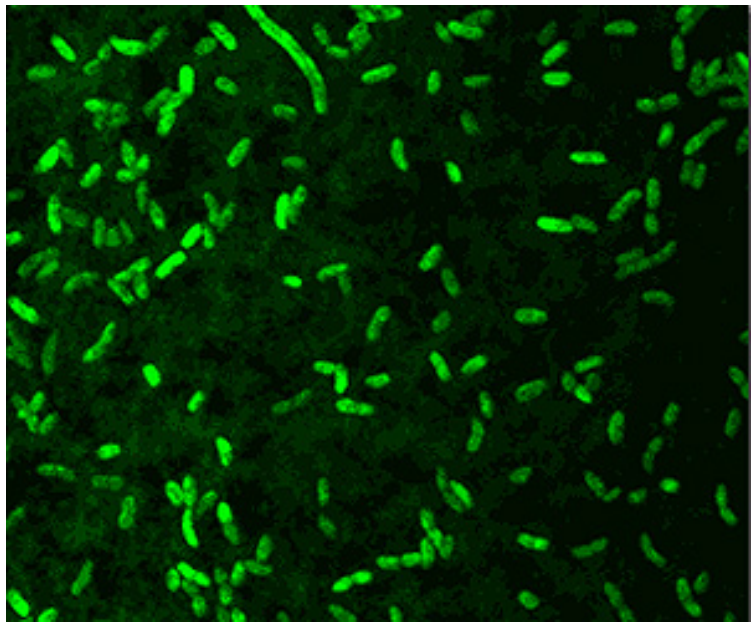
Group Behaviors

The marine bacterium Vibrio fischeri

It is a species of bioluminescent bacterium that exists naturally:

* Either in a free-living planktonic state.
* As a symbiont of a luminescent squid (**Hawaian squid, Euprymna scolopes**).

The marine bacterium Vibrio fischeri

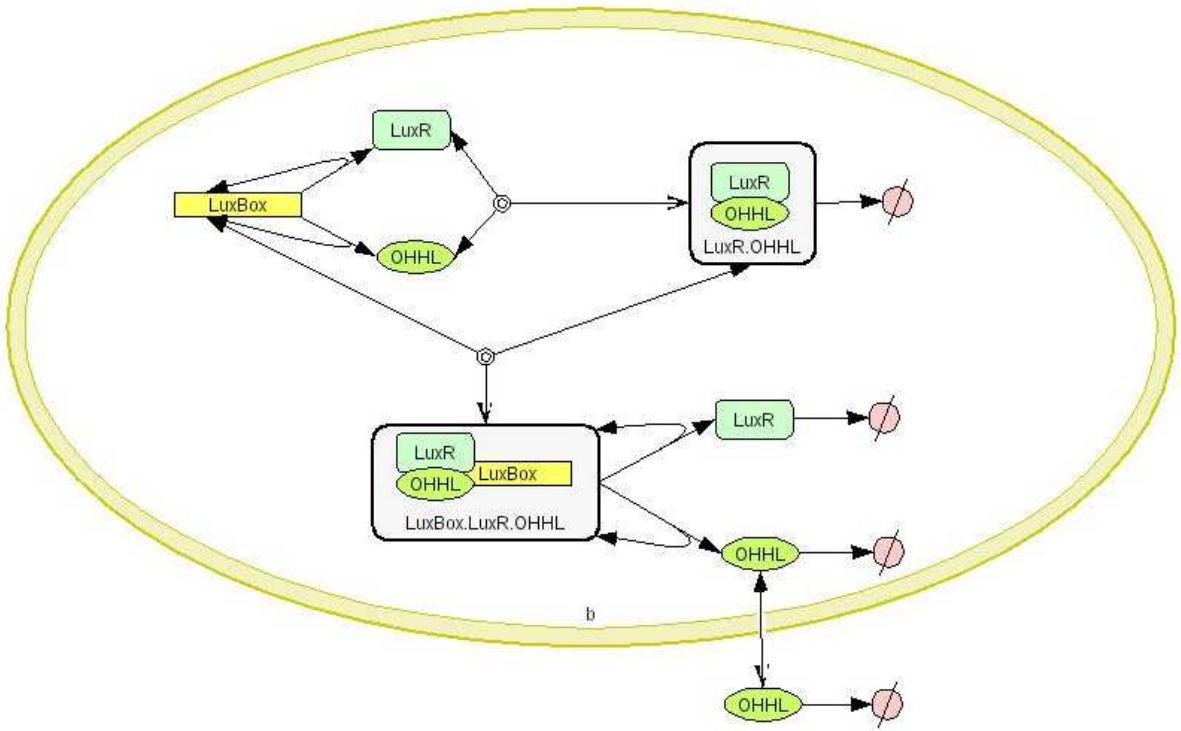


* Bacteria colonise specialised light organs in the squid, producing luminesce.
* It is involved in the attraction of prey, camouflage and communication between different individuals.
* The bacteria only luminesce when colonising the light organs and do not emit light when in the free-living state.

Quorum sensing in Vibrio fischeri

The **first computing model** of quorum sensing in bacteria was given in 2006[6]

- ⋆ In the framework of Membrane Computing (**multienvironment P systems**).



- ⋆ It was improved in 2008[7]

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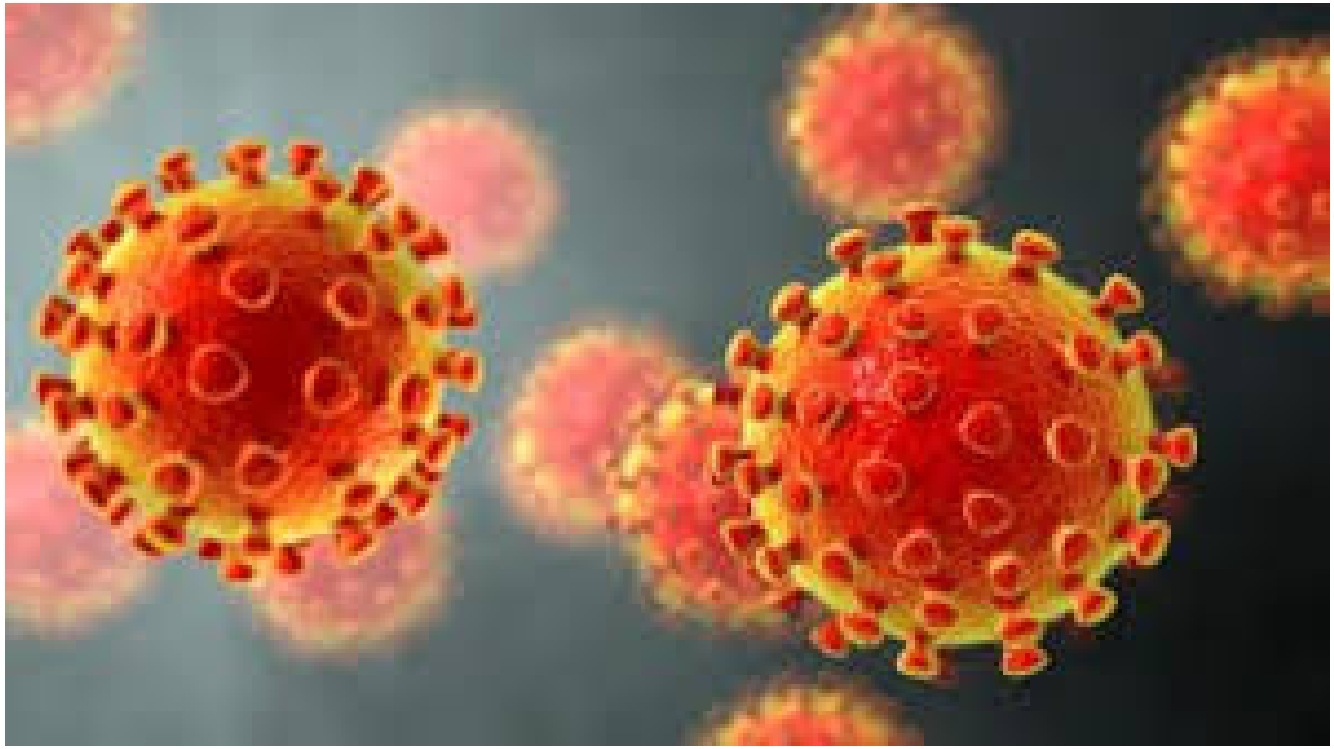
[6] M.J. Pérez-Jiménez, F.J. Romero: P Systems, a New Computational Modelling Tool for Systems Biology. **Lecture Notes in Bioinformatics**, **4220** (2006), 176-197.

[7] F.J. Romero, M.J. Pérez-Jiménez: A model of the Quorum Sensing System in Vibrio Fischeri using P systems. **Artificial Life**, **14**, 1 (2008), 95-109.

Viruses

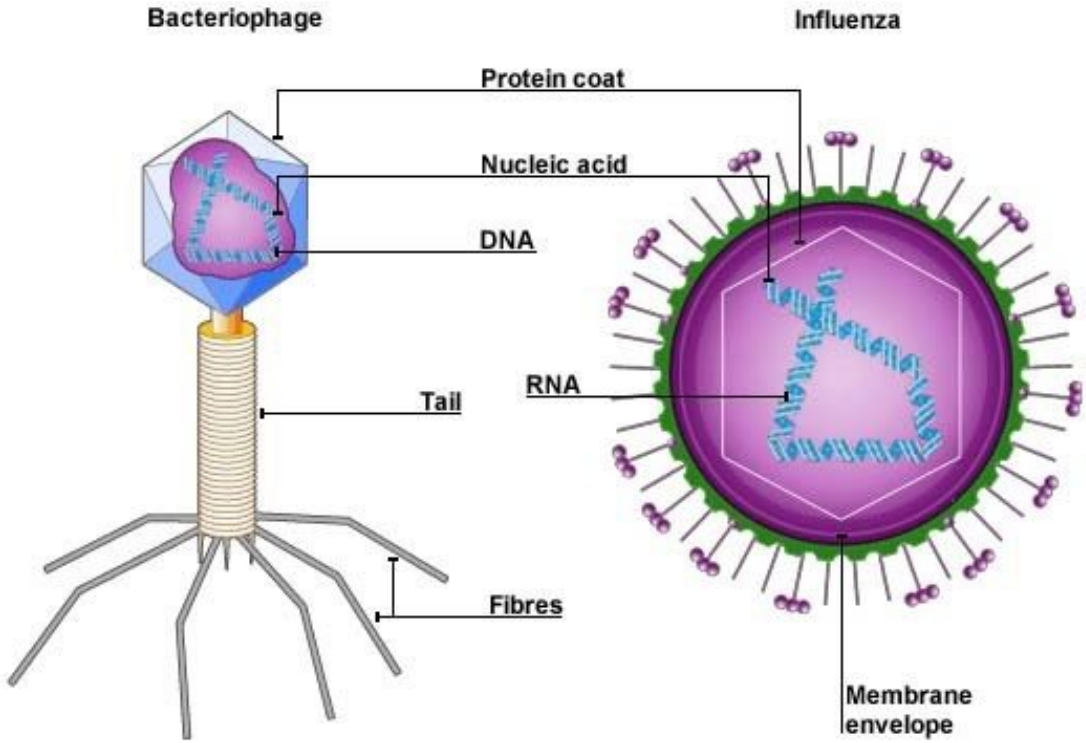


Small parasitic biological agents that cannot reproduce by itself.

- ⋆ The most abundant parasites on Earth.
- ⋆ They have not **independent** life (can only inhabit host species).
- ⋆ Viruses are not lone "wolves". They have **social lives**.

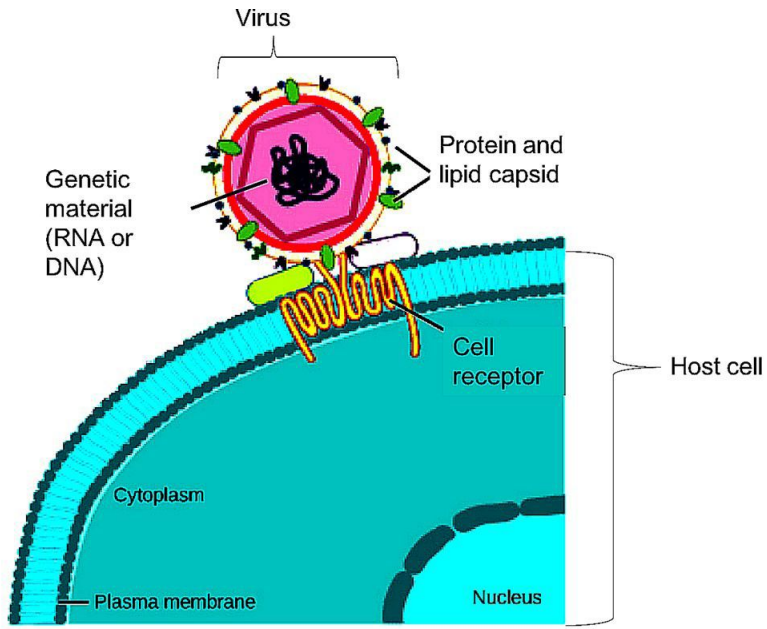
Viruses

A simple structure:



- ⋆ Genetic material: either RNA or DNA.
- ⋆ A protective protein coat.

Viruses



Viruses that infect bacteria (**phage**) have mechanisms that inform them about the possibility of remaining inactive or attacking (depending on new victims).

These processes are active: the phages seem to just sit back and listen in, waiting for bacterial signals to reach some threshold before taking action.

Viral replication

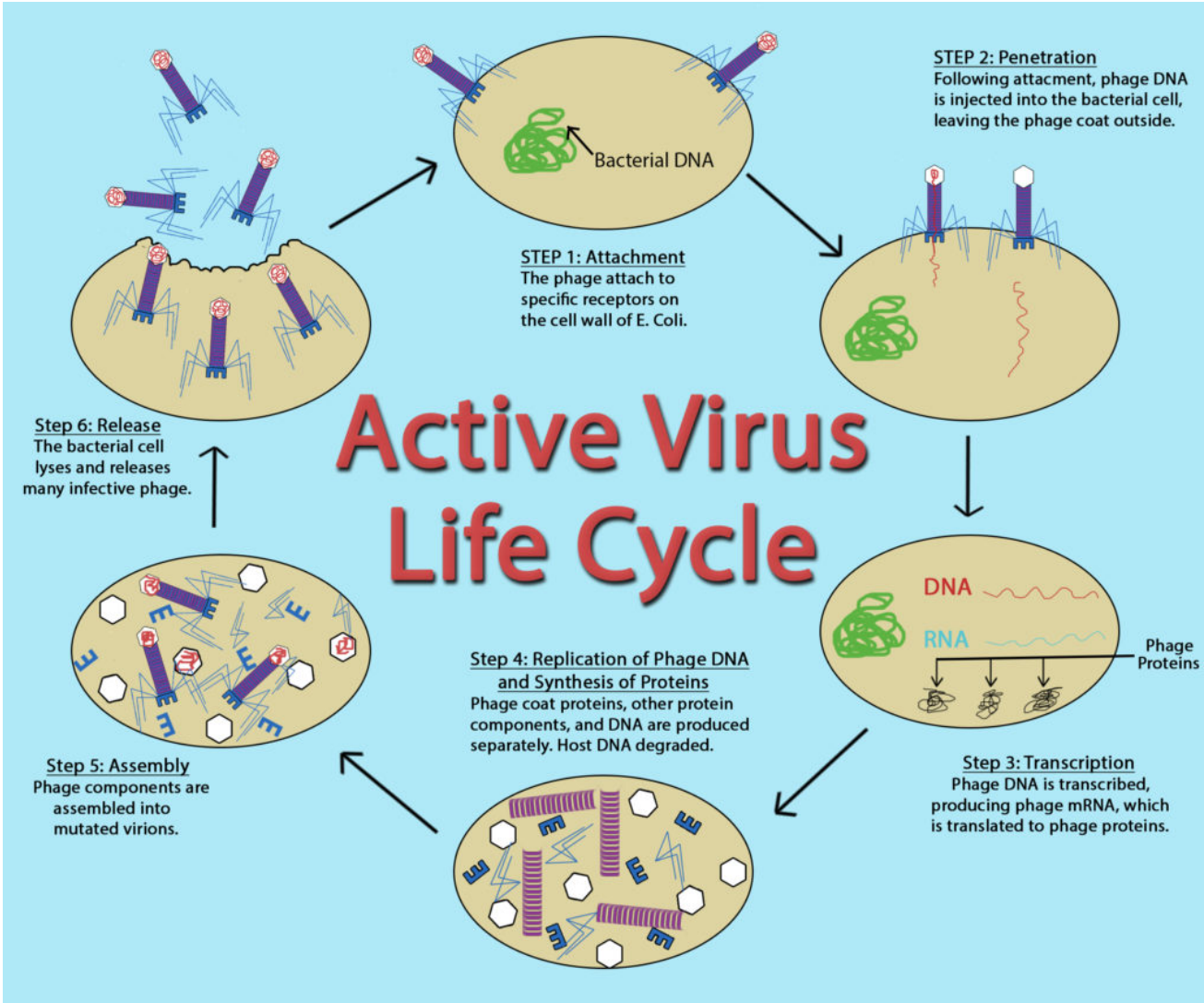
Three phases:

- ⋆ **Initiation of infection**:
- ⋆ **Replication and expression of the genome**.
- ⋆ **The release of the nature virions from the infected cell**.

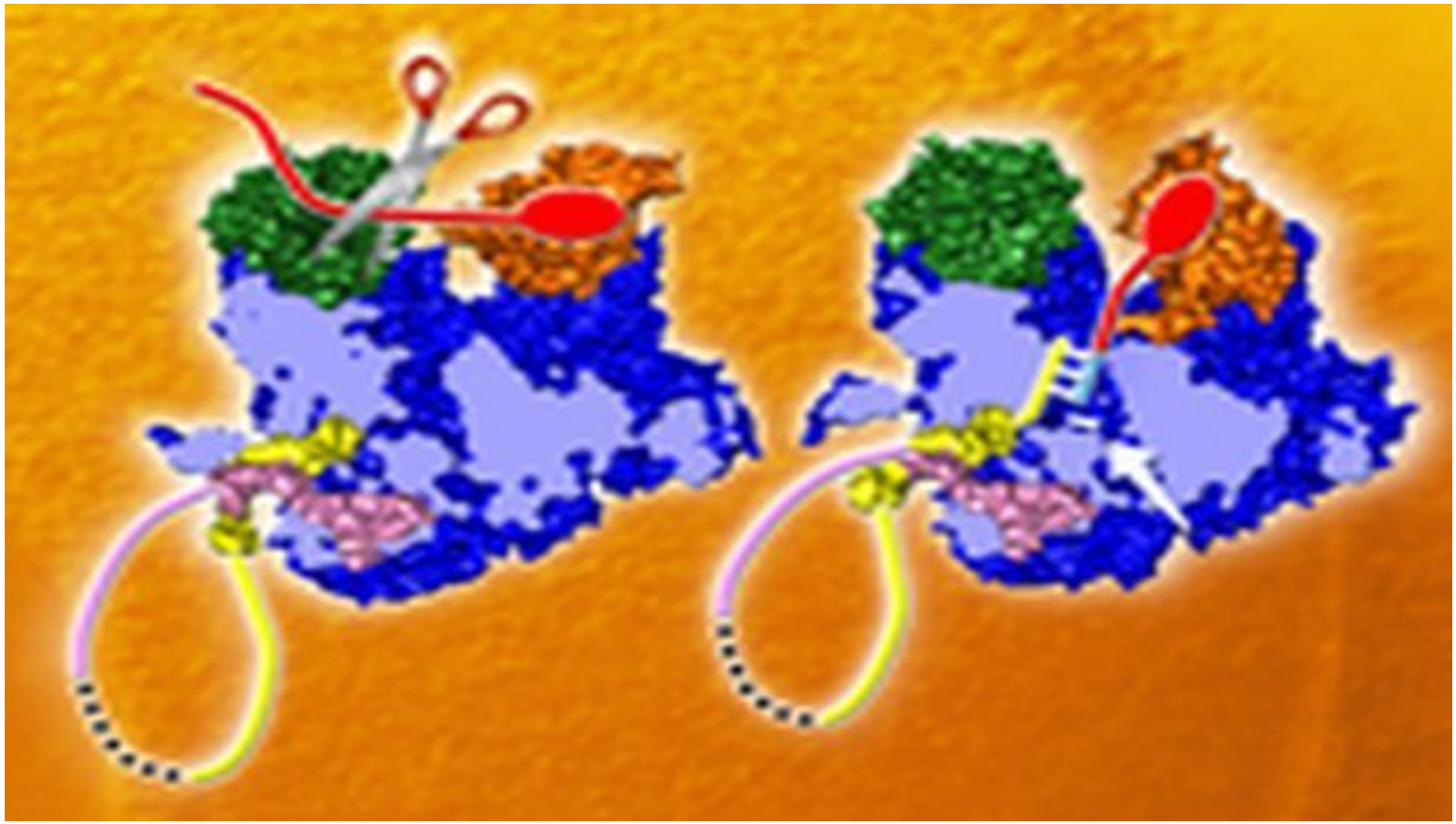
Viral replication

- **Initiation of infection**:
  - **Attachment stage**.
  - **Penetration stage**.
- **Replication and expression of the genome**.
  - **Transcription stage**.
  - **Replication stage**.
  - **Assembly stage**.
- **The release of the nature virions from the infected cell**.

Viral replication

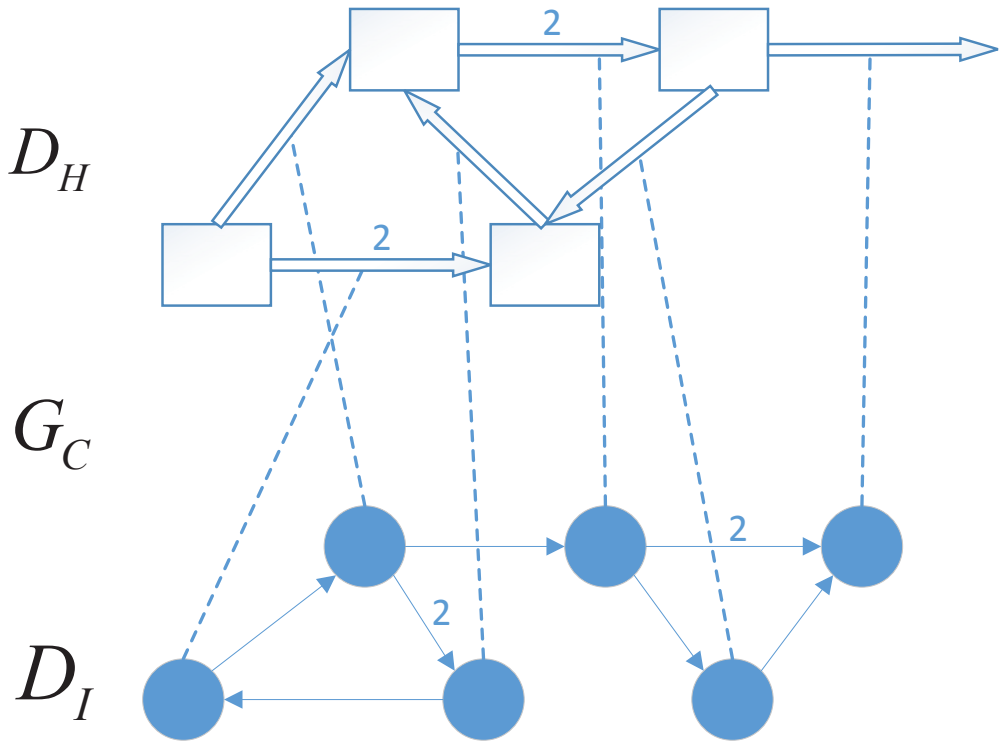


Virus machines



Virus machines

A new computing paradigm inspired by the manner in which viruses transmit from one host to another (introduced in 2015[8]).



[8] L. Valencia, M.J. Pérez-Jiménez, X. Chen, B. Wang, X. Zheng. Basic virus machines. In J.M. Sempere and C. Zandron (eds) **Proceedings of the 16th International Conference on Membrane Computing (CMC16)**, 17-21 August, 2015, Valencia, Spain, pp. 323-342.

Virus machines

The virus machines are equivalent in power to Turing machines[9].

They have the ability to:

- ⋆ **Generate** all **diophantine sets**[10]
- ⋆ **Compute** all **recursive functions**[11].

[9] X. Chen, M.J. Pérez-Jiménez, L. Valencia, B. Wang, X. Zeng. Computing with viruses. **Theoretical Computer Science**, **623** (2016), 146-159.

[10] A. Romero, L. Valencia, M.J. Pérez-Jiménez. Generating Diophantine Sets by Virus Machines. In M. Gong, L. Pan, T. Song, K. Tang, X. Zhang (eds) **Bio-Inspired Computing: Theories and Applications. The 10th International Conference (BIC-TA 2015)**, Hefei, China, September 25-28, 2015. Proceedings, pp. 331-341.

[11] A. Romero, L. Valencia, A. Riscos, M.J. Pérez-Jiménez. Computing partial recursive functions by Virus Machines. **Lecture Notes in Computer Science**, **9504** (2015), 353-368.

Pandemics

Pandemics

A pandemic is an outbreak of a disease that occurs over a wide geographic area and affects an exceptionally high proportion of the population.

The **SIR** mathematical model is an **ODEs based model**.

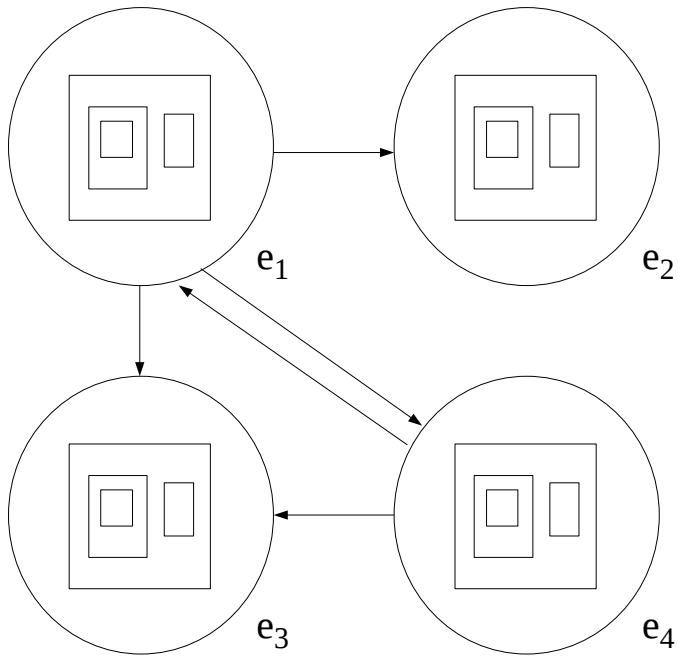
- ⋆ **S**: susceptible population.
- ⋆ **I**: infected population.
- ⋆ **R**: Recovered population.

A **SIR** computing model **based on PDP systems** [12] will be described.

[12] M.A. Colomer, M. Garcia-Quismondo, L.F. Macias, M.A. Martinez-del-Amor, I. Pérez-Hurtado, M.J. Pérez-Jiménez, A. Riscos, L. Valencia. Membrane system-based models for specifying Dynamical Population systems. In P. Frisco, M. Gheorghe, M.J. Pérez-Jiménez (eds.), **Applications of Membrane Computing in Systems and Synthetic Biology**. Emergence, Complexity and Computation series, Volume 7. Chapter 4, pp. 97-132, 2014.

Population Dynamics P systems

Network of processor units (**environments**), each of them containing a cell-like membrane system (share the same skeleton) with electrical charges associated with membranes and probabilities associated with the rules.



Pandemics: Our case study

Restricted to **three** physically separated **communities** (e.g. in different cities)

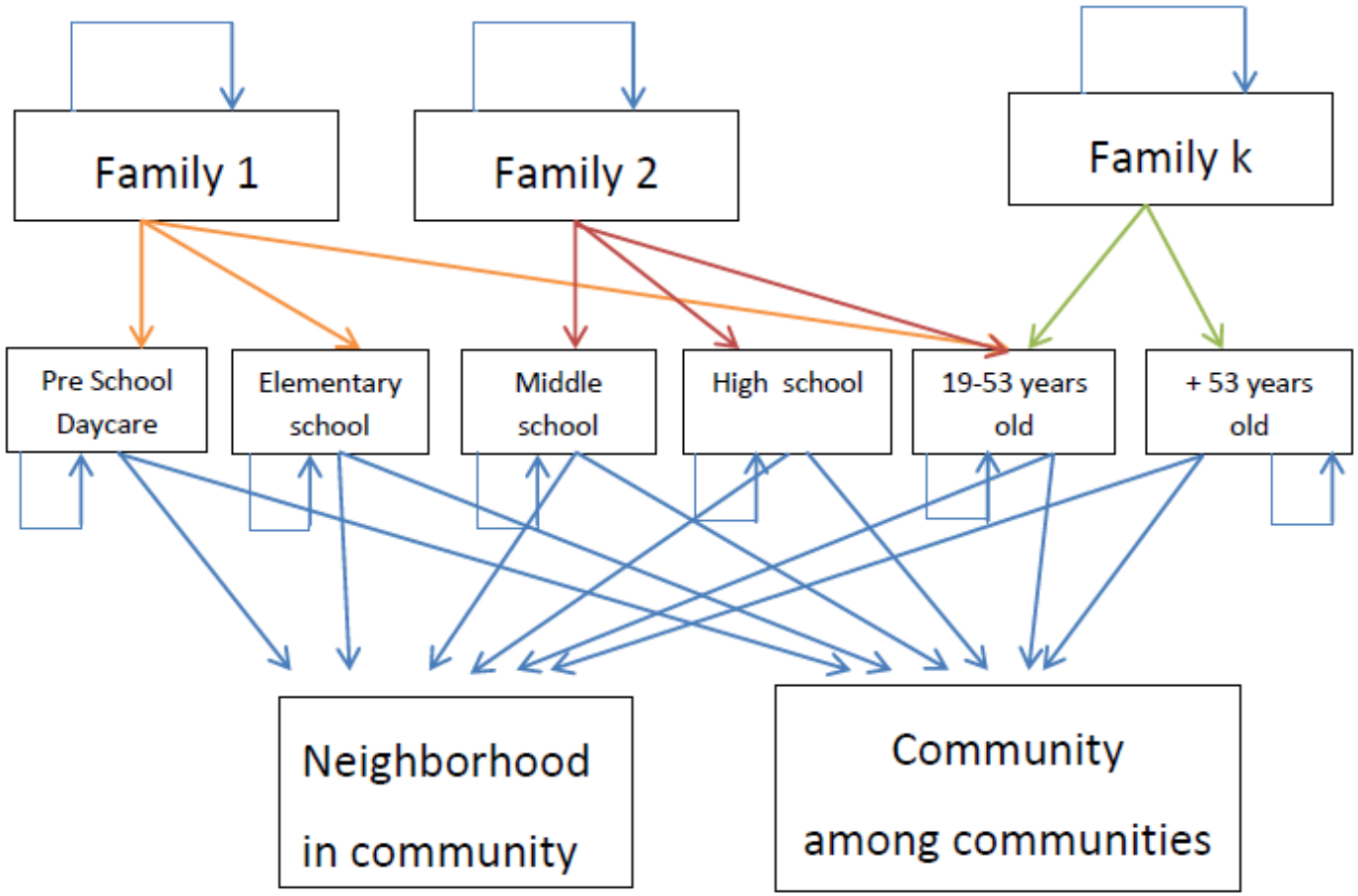
- ⋆ In each community, **four neighbourhoods**, where basic facilities for daily life are available.
- ⋆ Individuals in a neighbourhood are organized in **families**.
- ⋆ **Six groups** will be considered, **according to their age**: Daycares/Playgroups, Elementary schools, Middle schools, High schools, and two groups for Adults (19–53 years old, and over 53 years old).

A susceptible person can be infected either in the bosom of the family, at work, or in leisure time.

Human interventions are not taken into account.

Pandemics

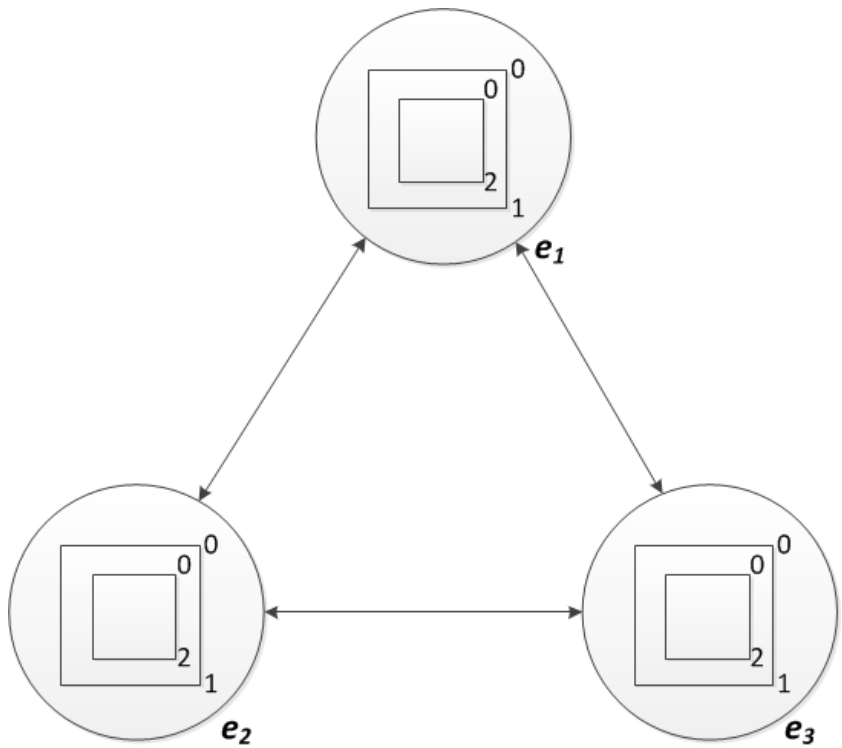
A network corresponding to interaction zones for each age group.



A PDP based SIR model

Computing model: a PDP with **three environments** and each of them containing a **P system of degree 2**.

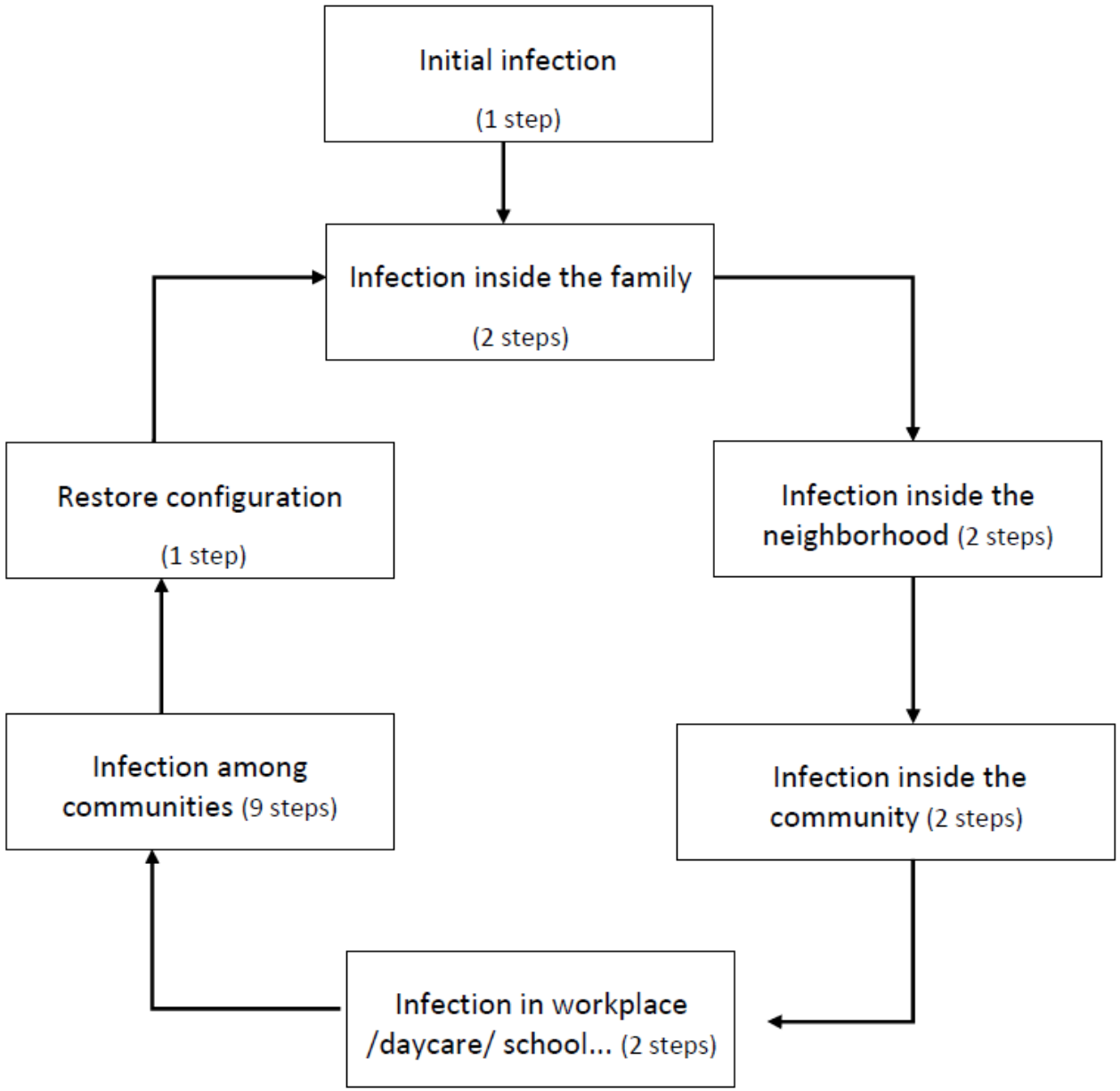
The network is described by the directed graph in the following picture:



Community in real life $\equiv$ **Environment** in the model

A PDP based SIR model

Modules of rules in the model:



Relevant symbols in the PDP based SIR model

- ⋆ $\mathbf{a_n}$: **individuals initially infected** in neighbourhood n ($1 \leq n \leq 4$).
- ⋆ $\mathbf{X_{f,g}}$, $\overline{\mathbf{X}}_{\mathbf{f,g}}$: **uninfected** and **infected individuals** (f= families, g= age groups).
- ⋆ $\overline{\mathbf{S}}_{\mathbf{f,g,i}}$, $\overline{A}_{f,g,i}$: **symptomatic** and **asymptomatic** individuals (i= days since infection; after at most 5 days, individuals will change status to recovered);
- ⋆ $\widehat{\mathbf{X}}$: to model the interactions of individuals infected by symptomatics ($S_{f,g}$) or asymptomatics ($A_{f,g}$).
- ⋆ $\mathbf{C_k}$: global clock controlling the evolution of the P system.

Description of the Initial infection

Generating the initial scenario, randomly distributing symptomatic and asymptomatic individuals along the system.

$\mathbf{I_{n,j}}$ (neighbourhood n, community j): multiplicity of object a_n that represents the initial amount of infected individuals on neighbourhood n, from community j.

These rules are only applied in the first step of the computation.

Each infected individual is estimated to interact with 20 other individuals during one day.

Rules associated with the Initial infection

* Generate symptomatic individuals

$$r_{1,f,g,i,n} \equiv [a_n \; X_{f,g} \xrightarrow{ps/4} \overline{S}_{f,g,i} \; \widehat{X} \; S^{20}_{f,g}]_2 \begin{cases} (n-1)F < f \leq nF, \\ 1 \leq g \leq 6, \\ 2 \leq i \leq 5, \\ 1 \leq n \leq 4 \end{cases}$$

ps: Probability for an infected person to be symptomatic.

f: families (F=number of families per neighbourhood);

g: age groups; i: days since infection; n: neighbourhoods.

* Generate asymptomatic individuals

$$r_{2,f,g,i,n} \equiv [a_n \; X_{f,g} \xrightarrow{(1-ps)/4} \overline{A}_{f,g,i} \; \widehat{X} \; A^{20}_{f,g}]_2 \begin{cases} (n-1)F < f \leq nF, \\ 1 \leq g \leq 6, \\ 2 \leq i \leq 5, \\ 1 \leq n \leq 4 \end{cases}$$

* Clock advance

$$r_3 \equiv [C_0 \longrightarrow C_1]_2$$

The PDP based SIR model: Experimental validation

Software tools used:

- **P-Lingua**[13]
  - A standard language to define P systems.
- **pLinguaCore Library**[13]
  - A Java library to manage P-Lingua files and simulate P system computations.
- **MeCoSim**[14]
  - A visual environment to perform the simulations.

[13] I. Pérez-Hurtado. **Desarrollo y aplicaciones de un entorno de programación para computación celular: P-Lingua. Ph.D. Thesis**, University of Seville, 2010.

[14] I. Pérez-Hurtado, L. Valencia, M.J. Pérez-Jiménez, M.A. Colomer, A. Riscos. MeCoSim: A general purpose software tool for simulating biological phenomena by means of P Systems. In K. Li, Z. Tang, R. Li, A.K. Nagar, R. Thamburaj (eds.) **Proceedings 2010 IEEE Fifth International Conference on Bio-inpired Computing: Theories and Applications (BIC-TA 2010)**, IEEE Press, Volume 1, September 23-26, 2010, Changsha, China, pp. 637-643.

An application for the PDP based SIR model

Virtual experiments have been performed:

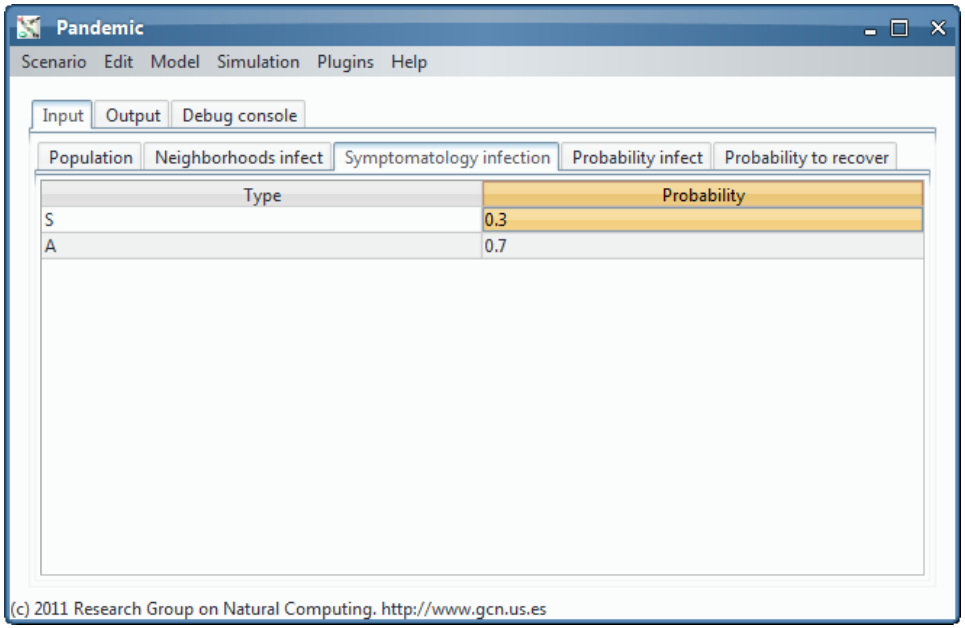
- By providing the general model for **SIR** in P-Lingua format.
- By introducing the appropriate values for the data corresponding to **different scenarios** in the input tables of the MeCoSim window.

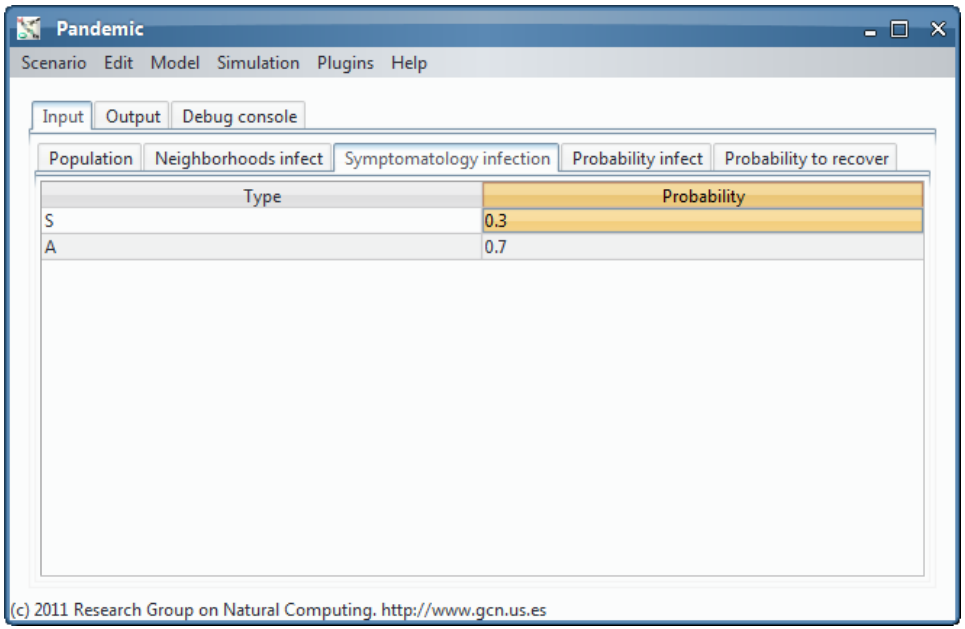
Three scenarios will be considered, all of them containing [15]:

- 3 communities and 20 families for each community.
- At the initial stage, there are
  - Community 1: 6 infected individuals.
  - Community 2: 0 infected individuals.
  - Community 3: 6 infected individuals.

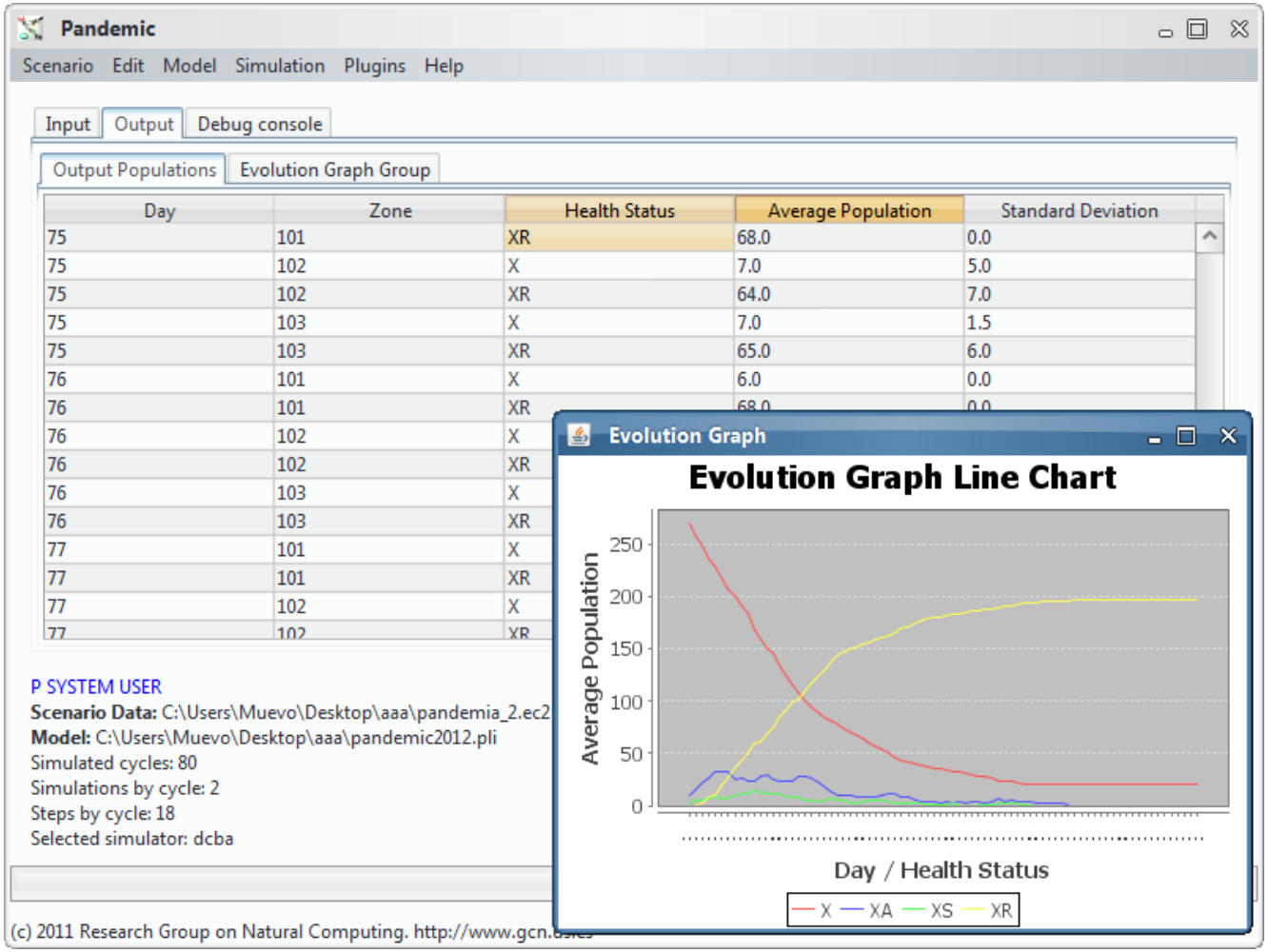
[15] H. Yasuda, K. Suzuki, Measures against transmission of pandemic H1N1 influenza in Japan in 2009: simulation model. **Euro Surveill**, 2009 Nov 5;14(44):19385.

Input tables





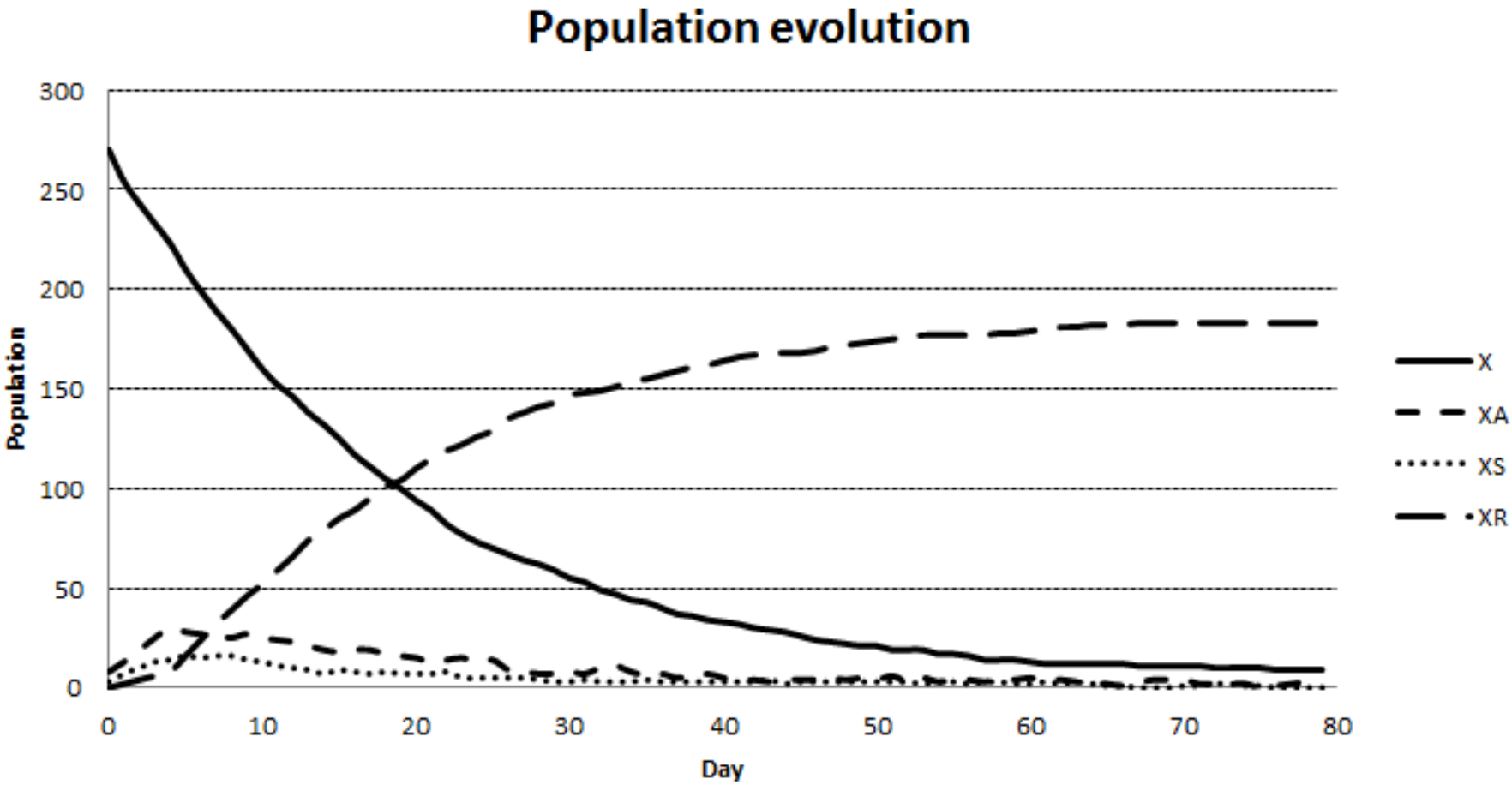
Output table



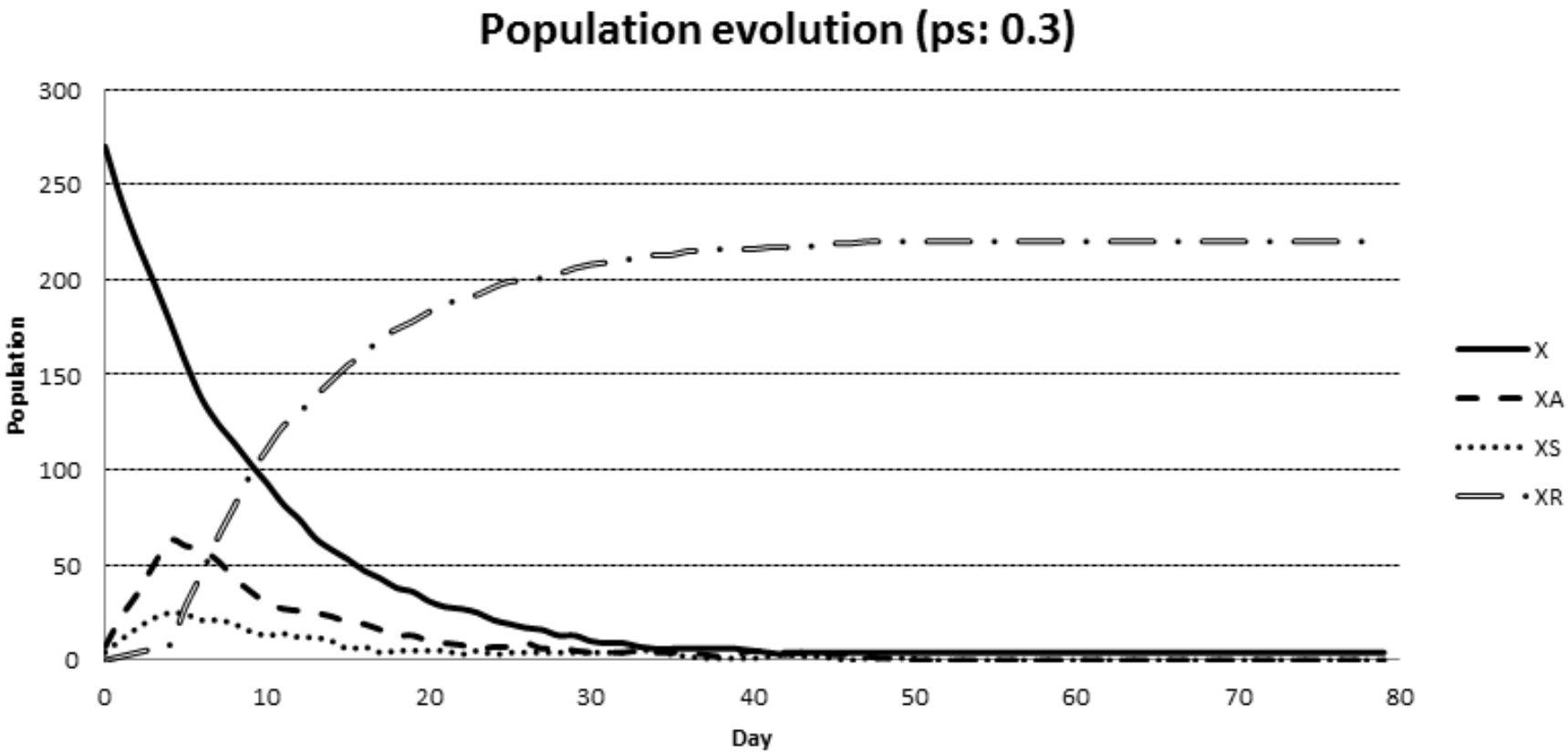
Scenarios

Probability	Scenario 1	Scenario 2	Scenario 3
For a susceptible person in contact with an infected one to become infected	**5%**	**10%**	**10%**
For an infected person to manifest symptoms (Symptomatics only can infect people inside their family but asymptomatics might infect people in other families and communities)	**30%**	**30%**	**10%**
For a symptomatic person to recover (asymptomatic people always recover)	**5%**	**30%**	**30%**

Virtual experiments: First scenario

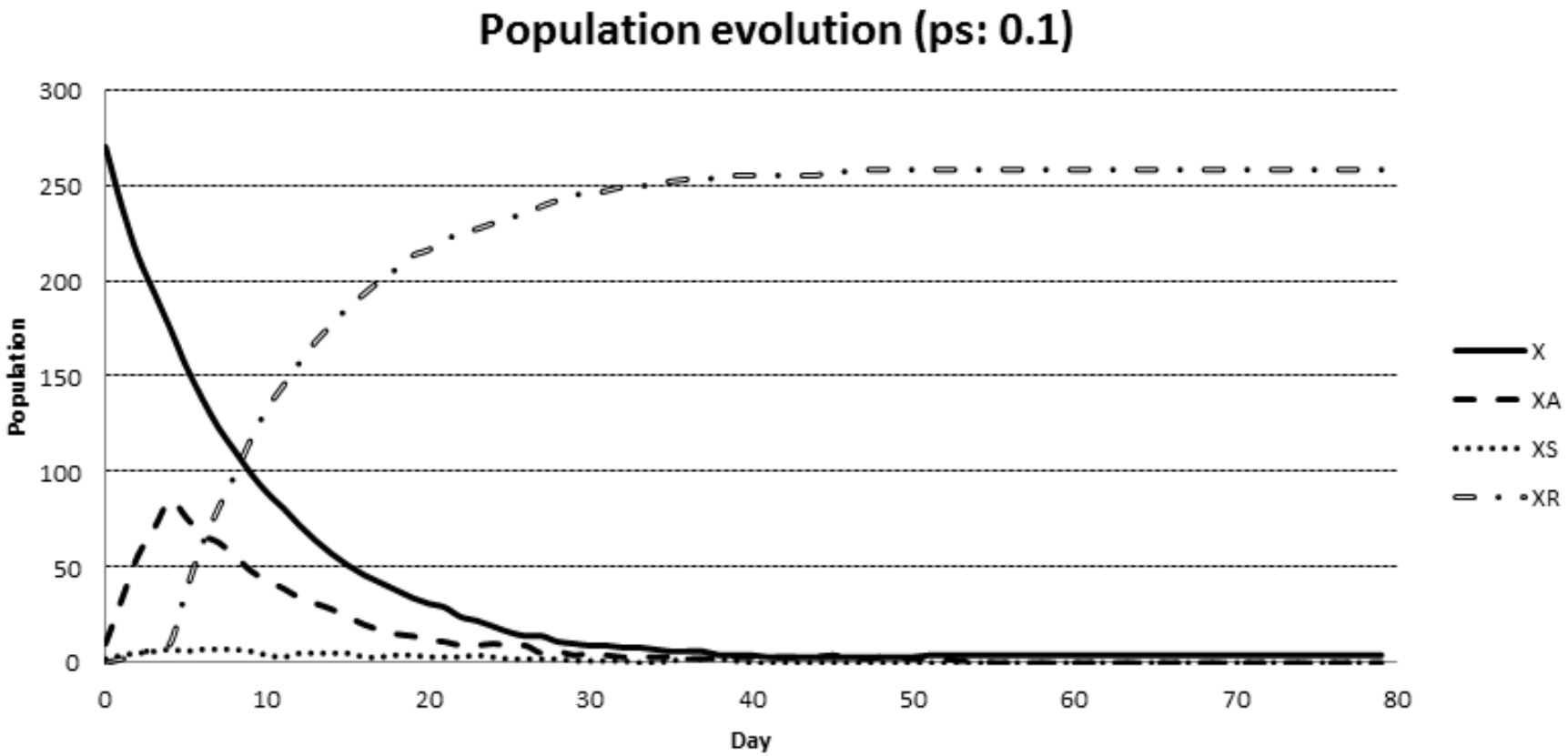


Virtual experiments: Second scenario

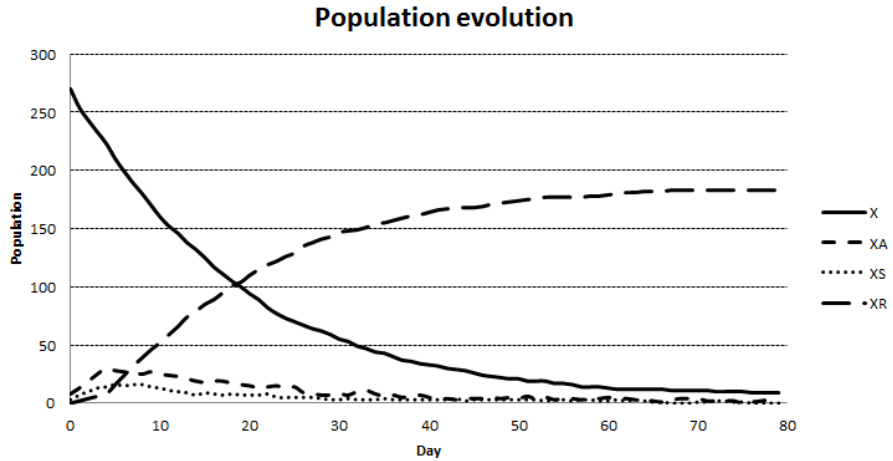


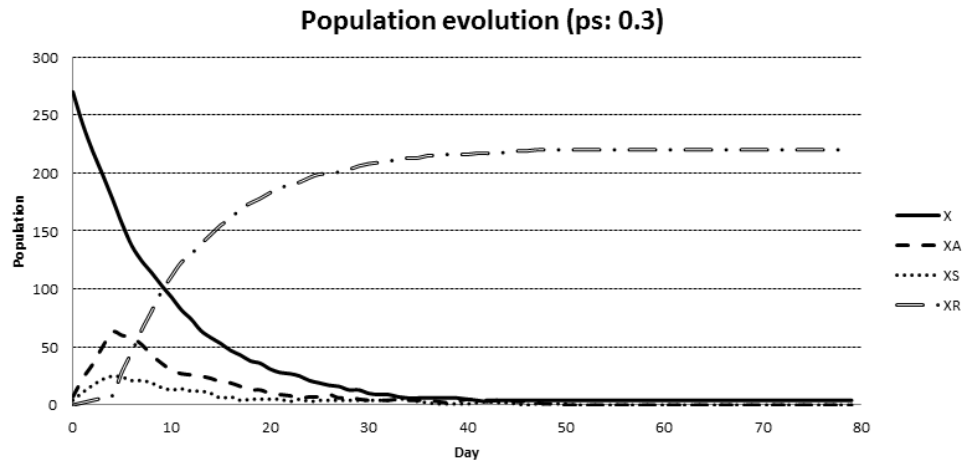
ps= Probability for an infected person to be symptomatic

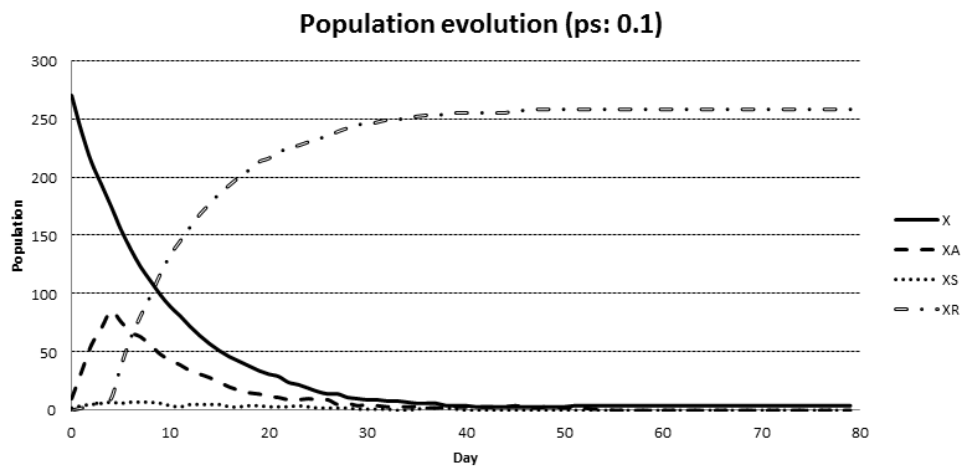
Virtual experiments: Third scenario



ps= Probability for an infected person to be symptomatic


Population evolution
Population
Day
X
XA
XS
XR


Population evolution (ps: 0.3)
Population
Day
X
XA
XS
XR


Population evolution (ps: 0.1)
Population
Day
X
XA
XS
XR

Conclusions

No significant differences among the three communities.

Third scenario presents a **bigger number of recovered** individuals.

The results of our simulations coincide with those obtained by using classical **SIR** models.

THANKS

FOR YOUR ATTENTION !