Investigating the Dynamics of Mass Action Systems

Oded Maler[1], Ádám Halász[2], Olivier Lebeltel[1], Ouri Maler

[1]CNRS-VERIMAG, University of Grenoble, Grenoble (France)

[2]Department of Mathematics, West Virginia University, Morgantown, WV (USA)

Traditional Mass Action

- In the standard molecular interpretation of chemical reactions, there are several *species, of molecules,* A,B,… .
  - The state of the system is defined by the number of molecules of each type, N_A , N_B , …
- Reactions are transformations where one, two, etc. molecules transform into *some other number* of molecules:
  - A → B, A+B → C, A→ B+C, A + B +C → D, ..
- The *rate* of a reaction is the probability per time associated with it.
  - For mass-action systems, the rate of a reaction is proportional to the product of concentrations (particle counts) of each species that enters on the left-hand side

Spatial Considerations

- Arguably the most often ignored, and hardest to tackle, aspect of bio-molecular processes is the fact that all processes take place in a spatially extended, not necessarily homogeneous environment.
- One of the lessons from the first 20 years of systems biology is that brute force doesn't work. There are good methods to describe spatially extended processes, thanks to the work of many physicists and chemists, but they are very expensive.
- The well known problems of biological modeling (lack of detailed parameter information and the extreme limitation on the ability to perform controlled experiments) are exacerbated when spatial issues come into play.

When Does Spatial Organization Matter?

- Yet, sometimes, simple models that ignore spatial aspects work just fine. Similarly to stochasticity (which can be safely ignored more often than not), it seems that situations where space *must* be taken into account are special.
- We propose a simple emulation of spatially distributed reaction-diffusion systems to help investigate these issues.
- A one-species reaction (A→ ..) can be seen as a "decay", the result of an intrinsic property of the input species. Such a reaction takes place independently of the distribution of A.
- By contrast, a two-species reaction (A+B→C) happens as a result of the collision of an A and a B molecule, which is why the rate is proportional to the number of possible (A,B) pairs. We expect that these reactions will depend on the distribution.

The Model

- The basic entity is a probabilistic automaton
- The number of automata is **fixed**
  - Agents may be in one of a finite set of states (q_1,q_2,..)
  - There are two kinds of state transitions
    - Spontaneous ($q_1 \rightarrow q_2$)
    - Induced by interaction with another agent ($q_1 \xrightarrow{q_2} q_3$)
- Transitions take place at fixed time increments
  - Each type of transition has an associated probability
  - Induced transitions only occur when the particle detects an encounter with another particle of the appropriate type

Not exactly mass action

- The main difference between standard mass action and our model is “causality”
  - In an (A,B) encounter, the effect of B on A is independent of the the effect of A on B.
  - As a result, the system can be updated in a “synchronous” manner, particle by particle
  - It can be shown that this is a subset of regular mass action rules
- The other difference is that agents are never destroyed nor created, they only change type.
- It is not yet clear whether our model can emulate an arbitrary mass action system (even restricted to uni- and bi-molecular reactions)

Aggregation styles

- Counting abstraction
  - Equivalent to the well-mixed case
  - We do not follow the position of agents
  - Interactions occur with an encounter probability, proportional to the number of possible partners.
- Further abstracted by allowing “fractional” agent counts
  - Such a simulation will predict (in some cases) the average behavior
  - There are important exceptions, such as in the case of multistable systems

Example

- An example specification:

δ	$\perp$			q_1			q_2			q_3		
q_1	0.9	0.1	0.0	1.0	0.0	0.0	0.7	0.2	0.1	0.7	0.0	0.3
q_2	0.1	0.8	0.1	0.0	0.6	0.4	0.0	1.0	0.0	0.1	0.9	0.0
q_3	0.0	0.0	1.0	0.7	0.0	0.3	0.3	0.4	0.3	0.0	0.0	1.0

- Each group or 3 columns gives the relative probability of transformation into (q1,q2,q3), upon meeting (nothing, q1, q2, q3).
- The relative rate of spontaneous transitions (1-α) also needs to be specified, for example α=0.1 corresponds to the following update rules:

$$
\begin{aligned}
x_1' &= x_1 - 0.09x_1 + 0.09x_2 - 0.06x_1x_2 + 0.08x_1x_3 + 0.08x_2x_3 \\
x_2' &= x_2 + 0.09x_1 - 0.18x_2 - 0.04x_1x_2 + 0.06x_2x_3 \\
x_3' &= x_3 + 0.09x_2 + 0.1x_1x_2 - 0.08x_1x_3 - 0.14x_2x_3
\end{aligned}
$$

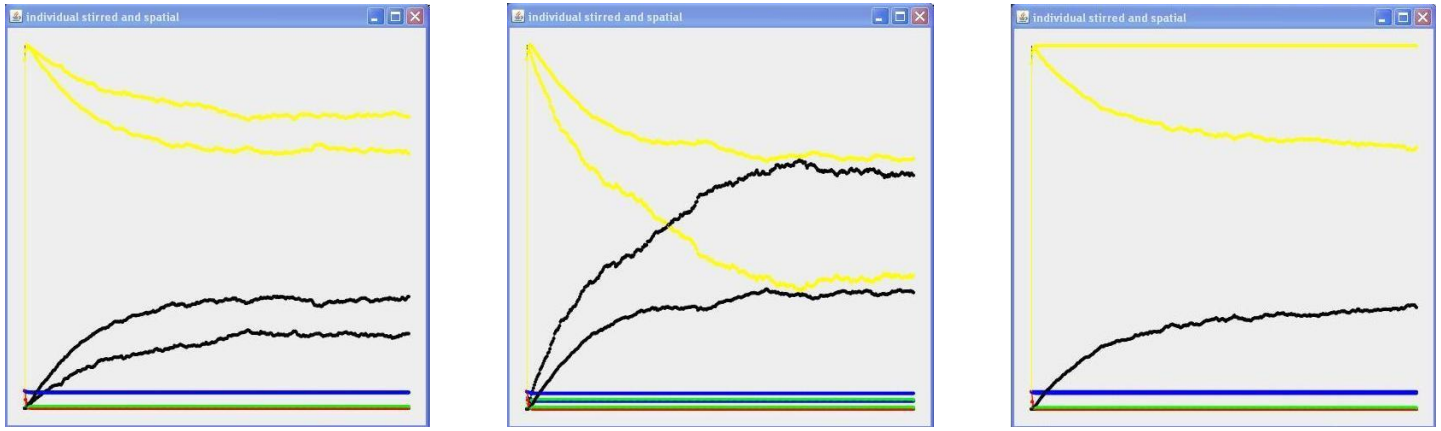
- Starting from x=(0.4,0.3,0.3), this gives convergence to (0.366, 0.195, 0.437).
- Rules corresponding to α=0.9 lead to convergence to (0.939,0.027,0.033).

Spatially distributed model

- The more interesting situation is when we endow our agents with a position:
  - At each update, agents generate a displacement vector according to a normal distribution (similar to Brownian diffusion)
  - For the state transitions, now each agent determines the agents that are close to it (within an **interaction radius**), and then selects one of them to implement the corresponding update rules.
- This model is similar to reaction-diffusion systems, with some important differences
  - The update rule is “deterministic” in the previously discussed sense
  - This allows for a more efficient implementation (no need to deal with pairs of agents, only a list of neighbors).

Spatial Simulations

- The model was implemented in Java.
- Preliminary experiments are aimed at identifying the effect of various initial spatial distributions on the final state of the system.

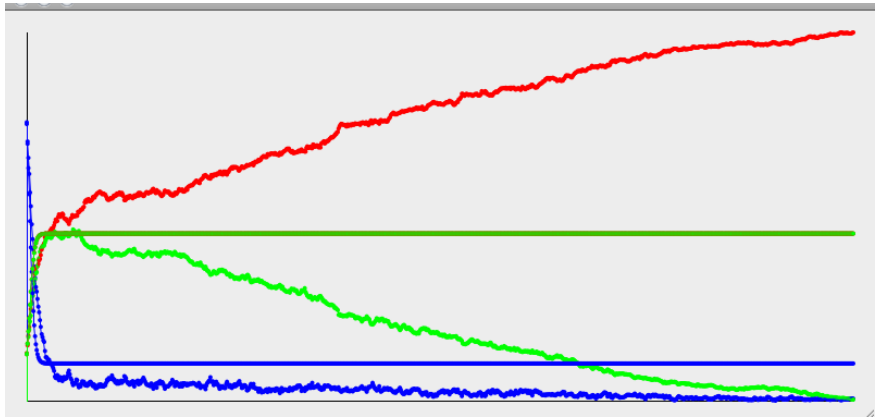


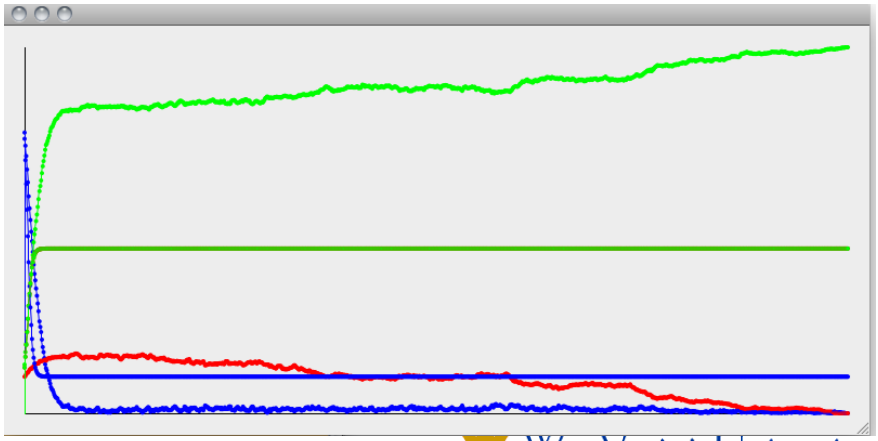
(a) (b) (c)

Figure 1: The evolution of the 5-species system where *A*'s and *B*'s are initially (a) distributed uniformly in space; (b) close to each other and (c) remote from each other. The plot depict the spatial and non-spatial models with the black curve indicating the growth of *E*.

Three colors

- Red competes with Green, Blue is neutral
  - Steady states are either all-Red or all-Green
- Same initial counts in all runs, different distributions
  - All colors uniform – can go both ways
  - Red concentrated over a small area or uniform – disadvantage for Red
- Principle of “gerrymandering”





Summary

- We defined a simplified model to study the effect of spatial distribution on reaction-diffusion systems
- Our model can be simulated efficiently, and analytical approaches also seem promising
- This model can be emulated by a regular mass action system, the reverse may also be possible in limited cases.
- When particles interact, initial configurations where different species are close together, separated, or spread out, lead to different final states.