Ecole de Porquerolles

Modélisation individu-centrée de systèmes biologiques complexes

Application à la simulation de l’évolution de réseaux génétiques bactériens

Guillaume Beslon

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Introduction

• Aim of the course (first part):
  – Modélisation individu-centrée de systèmes biologiques complexes
    1. Complexes ?
    2. Systèmes Biologiques complexes ?
    3. Modélisation individu-centrée ?
    4. Modélisation ?

• Who am I?
  – Guillaume BESLON (guillaume.beslon@liris.cnrs.fr)
  – Professor at the INSA-Lyon, LIRIS Lab. (Laboratoire d’Informatique en Image et Systèmes d’Information),
  – Head of the INRIA COMBINING Team
  – Director of the IXXI (Rhône-Alpes Complex Systems Institute)
  – Research topics: Individual-based modeling of complex biological systems (mainly evolution)
What is a complex system?

• Numerous definitions but general agreement on:
  – The structure of the system ("many elements")
  – Some subjective judgment (not always clearly accepted)
  – Something “emerges” (but no general agreement on “what is emergence”)
  – Something is dynamic and “self-organized”...

“A system is a complex system if it is made of a large number of interacting elements and if the dynamics of these interactions govern the behavior of the system, giving to it an appearance of unity from the point of view of an external observer.”
From complex systems to the science of complex systems

• We can (more or less) define a “complex system” but what is the “science of complex systems”
  – Any system is a complex system at some levels of description
  – Does it implies that “science of complex systems = science”?
  – Hope you’ll agree that it is absurd! (at least)

• How can you define a science?
  – E.g., Biology, Chemistry and Physics are all working on DNA
  – A science is not defined by its objects but rather by its questions

• The science of complex systems is NOT the science of systems that are complex!
  – It is the science of questions that are specific to complex systems
Back to the definition

“A system is a complex system if it is made of a large number of interacting elements and if the dynamics of these interactions govern the behavior of the system, giving to it an appearance of unity from the point of view of an external observer.”
Back to the definition

“A system is a complex system if it is made of a large number of interacting elements and if the dynamics of these interactions govern the behavior of the system, giving to it an appearance of unity from the point of view of an external observer.”

• So the question is:
  – Given the elements and their interactions, how can we quantify/understand/reproduce the appearance of unity?

• Two main questions can be derived from the central one:
  1. Description: What is the “unity” of the system? What are the elements? How can we describe both levels accurately?
  2. Understanding: What is the link between the dynamic of local interactions and the unity of the global system?
“Nothing in biology makes sense except in the light of evolution”
(Dobzhansky, 1973)
... And evolution is pragmatic

Biocomplexity?

<table>
<thead>
<tr>
<th>Scales</th>
<th>Number of elements</th>
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<tr>
<td>second</td>
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<tr>
<td>minute</td>
<td>10^6</td>
</tr>
<tr>
<td>year</td>
<td>10^12</td>
</tr>
<tr>
<td>纳米</td>
<td>10^9</td>
</tr>
<tr>
<td>纳米米</td>
<td>10^14</td>
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<tr>
<td>米</td>
<td>10^15</td>
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<tr>
<td>公里</td>
<td>10^16</td>
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</table>

<table>
<thead>
<tr>
<th>Heterogeneity</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>kind of proteins</td>
<td>10^6</td>
</tr>
<tr>
<td>kind of cells</td>
<td>10^3</td>
</tr>
<tr>
<td>species</td>
<td>10^7</td>
</tr>
</tbody>
</table>

nucleotides 5.10^9
genes 3.10^6
proteins 10^10
cells 10^14
neurons 10^12
humans 5.10^9
Biologie des systèmes complexes

• D'où vient l'apparence d'unité des systèmes biologiques ?
  – Biologie des systèmes, biologie intégrative, vie artificielle, ...

• Comment étudier cette « apparence » d'unité ?
  – Manque d'outils adaptés à la complexité des systèmes biologiques

• Démarche de modélisation (biologie « in silico »)
  – Quels modèles ?
  – Modèles individu-centrés (« description locale, observation globale »)
    • Par définition ces modèles manipulent un grand nombre d'éléments
    • Par définition ces modèles permettent d'explorer les interactions multi-échelles (mais rarement plus de deux niveaux d’organisation)
    • Malheureusement rarement (très) hétérogènes ...
    • Ils permettent un dialogue efficace (parlant) entre le modèle et la biologie (les biologistes)
What is a model?

• No clear definition (again!), strong polysemy
  – Models in science (formal sciences ≠ empirical sciences), models in art
• But always a clear link with idealization or imitation…

“To an observer \( B \), an object \( A^* \) is a model of an object \( A \) to the extent that \( B \) can use \( A^* \) to answer questions that interest him about \( A \).” (Marvin Minsky)

• So scientific models are instruments for scientific discovery
  – Used to explore properties of systems through virtual experiments
  – What is the epistemological status of a virtual experiment?
• Computational models are those which uses computation to perform the experiments
  – The model typically uses an algorithm to compute the state at type \( t \) from the state at time \( t-1 \)
Archipelago of models in complex systems science

[From Barthelemy, 2008]
What is IBM/ABM?

- Agent-Based Modeling is a kind of computational models based on an explicit description of the agents.
- “Bottom-Up” modeling:
  - Describe the system at the local level with some formalism
  - Simulate it (computational model)
  - Observe and analyze the results (at both levels!)

“In agent-based modeling (ABM), a system is modeled as a collection of autonomous decision-making entities called agents. Each agent individually assesses its situation and makes decisions on the basis of a set of rules. Agents may execute various behaviors appropriate for the system they represent -- for example, producing, consuming, or selling. Repetitive competitive interactions between agents are a feature of agent-based modeling, which relies on the power of computers to explore dynamics out of the reach of pure mathematical methods.”

[Bonabeau, 2002]
References


What is ABM?

• Agent-Based Modeling is more a methodology than a precise technique
  – You can choose the formalism you “want” at the agent level (dynamical models, set of rules, discrete/continuous coordinates, punctual particles or not, …)
  – The only thing you need is a way to compute the interactions and, thus, the resulting behavior
  • But this may not be a trivial question!
  – You’ll have to use computational tools that can be very diverse…

“Agent-Based Model is a mindset more than a technology.”

[Bonabeau, 2002]
What is ABM?

Individual-based modeling

Agent-Based modeling

Micro-simulation

Grid-worlds

Cellular automata

Multi-agent systems

Agent-Based modeling
What is ABM?

- Consensus for the principles
- Diversity of the appellations!
  - Micro-simulation (physics)
  - Agent-Based Modeling (computer science, social science)
  - Individual-Based Modeling (biology, ecology)
  - Bottom-Up simulation
- The only real difference is with MAS
  - Multi-Agent Systems are NOT Agent-Based Models
  - MAS are IT technologies trying to use CS approaches to improve the behavior of programs and computers
  - MAS are NOT models
  - MAS can be used to implement ABM but… why?
ABM, Cellular Automata and Grid Worlds

• 2D cellular automata are often presented as ABM
  – In CA rules are associated with the places, not with the agents
  – CA are not ABM, except when dealing with fixed agents (one place-one agent)

• Grid world are 2D worlds (sometimes 3D) where objects move on a grid-based space according to rules
  – The rules are local to the objects, not to the places
  – Probably the simplest ABM
  – E.g., DLA …
What is an agent?

• Classical definition (North & Macal)
  – A discrete entity/program with its own goals and behaviors
  – Autonomous, with a capability to adapt and modify its behaviors
  – Some key aspect of behaviors can be described.
  – Mechanisms by which agents interact can be described.

• Examples
  – People, groups, organizations, insects, swarms, robots…

• But this definition is strongly rooted in MAS and social systems
What is an agent?

• You will often find figures like:
What is an agent?

• An agent is (only) the unit of description of the micro-level
  – Again, “Agent” is more a methodological concept than a technological concept!
• What is agent (or not) depends on your point of view!
  – What is really important is what is local and what is not!
• It is often very difficult to decide what is an attribute, what is a memory, what is a resource …
  – E.g. xcor, ycor, speed, energy, …
What is an agent?

• Care the difference between:
  – “Anthropomorphic” definition: An entity that senses its environment and acts upon it in order to achieve a goal
  – Technical definition: A persistent autonomous software entity dedicated to a specific purpose (e.g. a program, a thread or a robot)
  – Methodological definition: The conceptual unit of interest, defines a boundary between what is modelled and what is observed (hum … often the observed system is the agent…)
Life-cycle of an ABM

- Developing an ABM seems straightforward!
  - Describe the system at the agent level; describe the interactions between the agents
  - Create a population of agents
  - Use some simulation method/software to let the agents and the population run
  - Observe the result(s)
  - Draw conclusion

- Actually it is (quite) as simple as this…
  - But some steps may be difficult ;(
Designing the agent level

• NOT YET: As in every model, define very carefully your system and your aim FIRST!
  – Generally a scientific question but…
  – ABM can also be used to help to define a scientific question!

• Choose the agent level, the agents behavior and the agent interactions
  – Take care: the devil is in the details!
  – You need a good knowledge and skill in order to be able to select the appropriate description at the appropriate level!
  – Care habits, transfer of models from a domain to another one, code reuse, …
  – Care implicit choices
How to design the agents?

• Actually no real methodology…
  – ABM skill helps,
  – A precise question helps a lot,
  – Domain knowledge helps enormously!
• The only methodology is trial and errors!
• Examples of agents
  – Molecules
  – Planets/stars
  – Humans
  – Insects
  – Companies
  – Cars
  – Drops of water
  – Birds…

Both have similar properties: inanimate objects following physical (Newtonian) laws

Can we use the same agents models?
How to choose the “level of complexity”? 
From agents to multi-agents

• Once you have designed the agents, you still have important choices to make
  – These choices are often forgotten (often implicit!)
• Agent will “live” in a spatio-temporal world
  – Real world is continuous
  – Agents’ world is not!
  – It creates risks and difficulties
• How to model time?
• How to model space?
The time model

• Time is often (always?) neglected in MAS approaches
  – Generally considered as a non-problem

• Discrete Time
  – Synchronous, asynchronous, discrete-events
  – What is the correct time step?
    • The higher the time step, the higher the error
    • The lower the time step, the slower the simulation
  – Practitioners are generally NOT able to estimate the correct time step of their systems!
  – The correct time step depends on the movement and on the interaction models

• The time model may strongly influences the global behavior
The space model

• Space is often at the core of ABM
  – Space is mainly a constraint on agents’ neighborhood
  – Very often, you will use ABMs to test the behavior of analytical models in a given spatial framework

• Lots of different space models are possible
  – From “Soup model” to GIS models
  – You often have to mix different space models (e.g. continuous space for agents + diffusion on a grid)
The space model

- Care: like for time, there are often implicit assumptions for the space model
  - Is 2D sufficient?
  - How to model the borders of the space?
    - Absorbing, reflecting, static, periodic…
  - How to model infinite spaces?

“Diffusion is not a perfectly mixing process in low dimension because the diffusing molecule will return to its initial position with probability 1, whereas, for $d > 2$, there is a significant probability that the diffusing molecule will never return to its origin.”

[berry, 2002]
Movement

- Agents will often move in “a” space
  - The laws of movement are generally supposed simple
  - Very often they are not!
  - Care not to reuse implicitly macroscopic laws of motion into a microscopic world (e.g., planets and molecules)
  - Sometimes the laws of motion explains the “emergent” results by themselves!

- E.G., DLA
  - Agents explore differently their vicinity depending on the laws of motion!
Fractals structures created by DLA

Two different laws of movement, which one is correct?
Law of motion matters!

- Coral morphogenesis [Merks et al., 2003]
  - Same agents
  - Different diffusion parameters leads to different shapes

Slow diffusion

Fast diffusion
Implementation step

• Once you have designed your agents and their relations, how can you implement them and run the simulation?
  – Plate-forms, frameworks,
  – Programming from scratch (which language),
  – Reuse a previous model

• Take care: the implementation phase is NOT the most difficult nor the most time consuming.

• Choose the methods/tools such that they
  – Respect the modeling phase
  – Will be efficient during the experimental phase
  – Enable to follow “strictly” a scientific experimental methodology

• Then, you’ll probably have to program “a little”…
Implementation

• You will often find figures like:
The pro&cons of visualization

• Complex systems are based on subjective judgment
  – We need a visual feedback!
• We often have no mean to decide what is correct and what is not
  – We need a visual feedback!
• We have to care natural interpretations
  – Care visual feedback! ("I like it!")
• We have to repeat the experiments
  – Visual feedback are often slow!
• We have to repeat experiments
  – Visual feedback cannot be aggregated
• Conclusion
  – Care to visualize easily and to emphasize what is important
  – Care not to focus only on visualization: data output are important
Experiments

• Agent-Based Models often have MANY parameters
  – Most of them are often implicit …
  – E.g., in my own model (Aevol) : 53 parameters!
• Agent-Based Models are generally slow
  – Need lots of computational resources
• It is NOT possible to test all parameters
  – Again, no hint! (except your own knowledge and experiments)
• Don’t explore randomly the parameter space
  – Use “good practices” of experimental science
  – Actually ABM is an experimental approach (digital experiments)
  – Having a laboratory notebook is a VERY good practice!
  – Log all your experiments ; finish all your experiments
• Making the model is often less “difficult” than running the model…
  – Plan resources and time from the beginning of your project
The meta-life-cycle of ABM

- Actually, ABM are not so difficult to build!
- The difficulty is (again) to produce knowledge with them!
- Meta-life cycle of ABM
  - Identify a good question
  - Build different simple models and play with them to identify what matters or not
  - Build YOUR model and make it stable
  - Make experiments with the model (experimental method helps!)
  - Analyze the results (statistical skill helps!)
  - Hopefully, acquire new knowledge (model the model)
  - Communicate, confront, publish
  - **FORGET YOUR MODEL**
Forget your model?

• Two reasons:
  • The model is not the knowledge
    “It could be argued that a criterion to determine good models is that they are no longer needed afterwards; The decisive thing with modeling is not the model per se, but what the model and working with the model does to our mind.”
    [V. Grimm, 1999]
  • Remember that a model depends on a question…
    – If you change the question you MUST change the model
    – Of course, you can reuse some pieces of software but be careful on implicit choice
    – The software is not the model
    – Take care not to jump steps in the meta-life-cycle!
So, is there a methodology?

• Definitely not
  – Modeling is an art
  – A counterfeiter is NOT an artist (though a skilled person!)

• But we can give hints
  – Be a VERY skilled with your modeling tools
  – Start from a good true question (i.e. that interests someone)
  – Be rigorous in your “experiments”
  – “Avoid the temptation to run tomorrow’s computer simulations before yesterday’s has been fully understood” (miller, 1995)
  – Use multiple complementary models rather than a big one
  – Confront your results with the specialists; (try to) publish in the journal they read
ABM validation

• Verification: The program is doing what you want it to do
  – Very difficult problem! (+/- software engineering)

• Validation: The model produces the “correct” behavior
  – Impossible problem: A model is never “valid”

“Essentially, all models are wrong, but some are useful.”
[G. Box]

• Actually it depends on what you want to do with the model!
  – Predictive models can be tested (but never proved!)
  – Scientific models generally cannot
  – A good model is a model that enables me to construct a scientific discourse
# Applications

Table 1: Agent-based Modeling Applications

<table>
<thead>
<tr>
<th>Business and Organizations</th>
<th>Society and Culture</th>
<th>+ evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Manufacturing</td>
<td>• Ancient civilizations</td>
<td>+ hydrology</td>
</tr>
<tr>
<td>• Consumer markets</td>
<td>• Civil disobedience</td>
<td>+ membrane models</td>
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<tr>
<td>• Supply chains</td>
<td>• Social determinants</td>
<td>+ soil models</td>
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<td>• Insurance</td>
<td>• Organizational networks</td>
<td>+ agriculture</td>
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<tr>
<td>Economics</td>
<td>Military</td>
<td>+ diffusion of innovation</td>
</tr>
<tr>
<td>• Artificial financial markets</td>
<td>• Command &amp; control</td>
<td>+ …</td>
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<tr>
<td>• Trade networks</td>
<td>• Force-on-force</td>
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<tr>
<td>Infrastructure</td>
<td>Biology</td>
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<td>• Electric power markets</td>
<td>• Ecology</td>
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<td>• Hydrogen economy</td>
<td>• Animal group behavior</td>
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<td>• Transportation</td>
<td>• Cell behavior</td>
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<td>Crowds</td>
<td>• Sub cellular molecular behavior</td>
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<tr>
<td>• Human movement</td>
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<tr>
<td>• Evacuation modeling</td>
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</table>

Note that businessmen are not as “narrow-minded” as scientists ;)

No need of “proofs”, just need to sell!
Grand challenge of ABM

Fusion/fission of agents
When/why using ABM?

- [Grimm, 1999]
  - Pragmatic motivation: ABM can model phenomenon impossible to model with other approaches (“another tool in the modelers toolbox”)
  - Paradigmatic motivation: State variables modeling gives a false vision of reality since individuality, discreteness, locality or space matter

- Hum, not clear … real motivations are more basic
  - Easy to construct, manipulate and extent (easy to change/add/remove parameters, rules,...) ... to easy?
  - Can model unknown phenomenon (if you have knowledge at the lower level)
  - ABM use a domain-based ontology (they are good interfaces between disciplines) easy to describe and to explain ... too easy?
  - “Looks like” (pleasant models) ... too pleasant?
Why/when using ABM?

• Very often, it is claimed that ABM must be used when analytical models fail but
  – Analytical models have a long history in ~every scientific domain (are you sure they fail?)
  – Can we (computer scientists) really know when analytical models can or cannot be used

• In practice, always try to use ABM in parallel with analytical models…
  – ABM can be use before analytical model (to propose hypothesis)
  – ABM can be used after analytical model (to validate hypothesis)
ABM vs. Analytical models
The BIG risk!
Another BIG risk!
The BIGGEST risk!
The future of ABM?
Retour à la vraie question !

- L’usage des modèles en science est tout sauf clair …
- Le modèle est intimement lié à l’imitation, à l’analogie, à la ressemblance
  - Mais il peut représenter aussi bien l’objet à imiter que l’imitation de l’objet ou un intermédiaire entre l’objet et l’imitation …
  - Modèles comme médiateurs …
- La modélisation est souvent considéré comme une démarche interdisciplinaire …
  - Pourtant, chaque discipline a sa propre conception des modèles …
  - Les modèles sont souvent à l’interface entre sciences appliquées et sciences expérimentales …
  - Dialogues de sourds autour des modèles (e.g. modèle de données, modèles d’objets)
  - Modèle normatif/modèle descriptif …
Qu’est-ce qu’un modèle ?

• Définitions « courantes » :
  – Ce qui sert ou doit servir d’objets d’imitation pour faire ou reproduire quelque chose,
  – Personne ou objet dont l’artiste reproduit l’image,
  – Objet, fait, personne possédant au plus haut point certaines qualités et caractéristiques et à laquelle peuvent se rapporter des faits ou des objets réels,
  – Objet, type déterminé selon lequel des objets semblables peuvent être reproduits en de multiples exemplaires,
  – Objet de même forme qu’un autre objet mais exécuté en réduction
  – Représentation simplifiée d’un processus, d’un système
Qu’est-ce qu’un modèle ?

« To an observer $B$, an object $A^*$ is a model of an object $A$ to the extent that $B$ can use $A^*$ to answer questions that interest him about $A$. »

Marvin Minsky

• Définition très permissive : est-ce que tout est modèle ?
  – Non : le modèle doit *servir* à produire de la connaissance …
  – Le modèle est donc un instrument scientifique
  – Il doit être utilisé *comme* un instrument
  – Est-il un instrument comme un autre ?
  – Non : selon la définition c’est un instrument personnel

• Paradoxe : si le modèle est un instrument, il doit être accepté par une communauté scientifique …
  – Le modèle doit être considéré comme un instrument valide …
  – Il doit se conformer aux pratiques scientifiques correspondant au champs d’étude de $A$ (et de $B$ ? Et de $A^*$ ?)
  – Mais chaque modèle est un instrument différent …
Une pièce à deux faces

- Le modèle est un instrument personnel
  - En ce sens son usage est TRES permissif …
- Le modèle est un instrument collectif
  - En ce sens son usage est TRES restrictif …
- Dans les deux cas son usage est très dangereux
  - Car en tant qu’instrument systématiquement nouveau, il doit être faire systématiquement ses preuves (et non faire preuve) …
  - Risque personnel (preuve insuffisante ou fausse)
  - Risque collectif (preuve non reconnue par la communauté)
- Or, la modélisation a toujours un caractère interdisciplinaire
  - L’usage individuel et l’usage collectif peuvent être conduits au sein de disciplines différentes …
  - En particulier dans les systèmes complexes …
Un instrument personnel

• Comment le modèle peut-il « faire preuve »
  – « Ce qui est simple est toujours faux. Ce qui ne l’est pas est inutilisable » (P. Valery)
  – « The decisive thing with modelling is not the model per se, but what the model and working with the model does to our mind » (V. Grimm, 1999)
  – « It could be argued that a criterion to determine good models is that they are no longer needed afterward » (V. Grimm, 1999)

• Le modèle ne fait donc jamais preuve
  – Mais ça n’interdit pas son utilité

• C’est le modélisateur qui incarne le lien entre le modèle et l’objet modélisé
  – Mais cela ne suffit pas …
Un instrument personnel

• Le modèle est indissociable de sa conception et de son utilisation (i.e., de son interprétation)
  – « La connaissance-projet se produit – et se représente – par conception de modèles (...) et non plus par analyse. Le modèle alors, qu'il soit iconique ou symbolique, devient source de connaissance et non plus résultat. Il ne décrit plus, ex-post, une connaissance-objet tenue pour ex-ante ; il représente a priori une connaissance-projet qui n'existe que par lui. » (J.-L. Le Moigne, 1987).

• Le modèle n’est donc pas un résultat, un objectif scientifique en soi
  – Le modèle n’est pas une (simple) copie

• Il n’est modèle que par rapport à une question sur un objet et par rapport à un interprète …
  – On ne peut pas dissocier le modèle du modélisateur …
  – Pourtant la pratique scientifique nous impose de communiquer le modèle à une communauté
Un instrument collectif

- Le modèle est un instrument personnel mais qui doit autoriser les échanges avec le collectif …
  - Sinon, risque de dérive intuitionniste …
  - La science qui se fait est la science qui se communique …
  - A qui ?
  - Que doit-on communiquer ? Le modèle, l’intuition ou la « conclusion » ?
  - La communication change-t-elle le statut du modèle ?

- « Il y a peu de controverses entre simulateurs car il y a peu de travail collectif. Les simulateurs sont rassemblés par l’équipement informatique qui leur est nécessaire, mais ils fonctionnent plutôt à la manière de petits artisans : chacun son problème, son modèle, son programme » (I. Stengers et B. Bousaude-Vincent, 2003)
Un instrument collectif

• Chaque champ d’application, chaque domaine scientifique, va exiger du modèle (et du modélisateur) qu’il se plie aux règles (implicites) du domaine
  – Sous peine de ne pas être considéré comme un instrument valide
  – Qu’est-ce qui fait la validité d’un instrument ?
  – Un modèle peut-il être un instrument valide puisqu’il est toujours un instrument ad-hoc ?
  – Attendez-vous à devoir convaincre …

• Le modèle doit être intégré à la connaissance du domaine et non à la connaissance « des modèles »
  – Imagine-t-on Galilée communiquer ses résultats uniquement à des opticiens ?
  – Galilée a du convaincre que les lois de l’optique sont valides pour l’astronomie
  – Le modèle doit définitivement s’insérer dans la pluridisciplinarité …
Inter- pluri- trans-disciplinarité

• Modéliser implique de dépasser les frontières traditionnelles entre les disciplines scientifiques
• Des collaborations sont indispensables
  – Expérimentateurs/modélisateurs, spécialistes du local/du global
  – Méthodes issues de champs disciplinaires différents
  – Questions issues de champs disciplinaires différents
L’inter-pluri-trans-disciplinarité est souvent défendue ... dans les discours
- Beaucoup plus rarement en pratique
- E.g. : « Je ne prends que les meilleurs » ...

Traverser les frontières entre disciplines scientifiques est difficile ! Cela demande du temps, du tact et cela implique des risques !
- Soyez modestes : toutes les disciplines sont TRES avancées
- Soyez tolérants : toutes les disciplines ont des habitudes (bizarres ;)
- Soyez clairs : quel est votre objectif ? Qui voulez-vous convaincre ? (où voulez-vous publier ?)
- Ne croyez jamais pouvoir apporter une connaissance de l’extérieur d’une discipline!

“The burden of proof is on us to explain our results to biologists in their own language and in their our journals”

[Miller, 1995]
Ecole de Porquerolles

Modélisation individu-centrée de systèmes biologiques complexes

Application à la simulation de l’évolution de réseaux génétiques bactériens

Guillaume Beslon
INSA – INRIA – LIRIS – IXXI
Introduction

• Aim of the course (first part):
  – Application à la simulation de l’évolution de réseaux génétiques bactériens
    1. Evolution ?
    2. Simulation de l’évolution ? (digital genetics)
    3. Simulation de l’évolution de réseaux génétiques

• Who am I?
  – Guillaume BESLON (guillaume.beslon@liris.cnrs.fr)
  – Professor at the INSA-Lyon, LIRIS Lab. (Laboratoire d’Informatique en Image et Systèmes d’Information),
  – Head of the INRIA COMBINING Team
  – Director of the IXXI (Rhône-Alpes Complex Systems Institute)
  – Research topics: Individual-based modeling of complex biological systems (mainly evolution)
Evolutionary systems biology?

• Every biological system is the result of an evolutionary story:
  – Understanding the story may help to understand the system

• Systems biology aims at explaining the global structure and organization of biological systems
  – +/- reverse engineering applied to biological systems
  – BUT: in reverse engineering, we have clues on the aims/wills/wishes/methods of the engineers
  – We don’t have such clues in the case of biological systems
  – Our “natural interpretations” are likely to be false (care anthropomorphisms…)
  – “Evolutionary systems biology” can guide us, help us avoiding natural interpretations, give the organization clues …
ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE
FOR LIFE.

By CHARLES DARWIN, M.A.,

FELLOW OF THE ROYAL, GEOLOGICAL, LINNEAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE
AROUND THE WORLD.'

LONDON:

JOHN MURRAY, ALBEMARLE STREET.

1859.

The right of Translation is reserved.
Evolution in two words

“Evolution will occur whenever and wherever three conditions are met: replication, variation (mutation), and differential fitness (competition).”

[Daniel Dennett]
Genetic variability
Natural selection

The **fitness** measures the probability of survival and reproduction.
Example of “natural” evolution

- *Biston betularia* (Peppered moth)
  - 1848: first (known) occurrence of the black morph (*carbonaria*)
  - 1898: *carbonaria* represents 98% of the population (industrial melanism)
Example of “natural” evolution

- *Biston betularia* (Peppered moth)
  - 1848: first (known) occurrence of the black morph (*carbonaria*)
  - 1898: *carbonaria* represents 98% of the population (industrial melanism)
Introduction

• Although it can be described in a few words, evolution give rise to many complex phenomenon that can be very difficult to understand
  – Evolution of cooperation, evolution of sex, evolution of complexity…

• Evolution is difficult to study
  – Well known snapshot (today)
  – Few fossil records
  – Difficult experiments

• Some evolutionary pressures are well-known but their relative contribution is almost impossible to assess
  – Modeling needed!
The fitness landscape metaphor
(Sewall Wright, 1932)
The fitness landscape metaphor

Fitness

“Kind of”
The fitness landscape metaphor

Fitness

Mutation

“Kind of”
The fitness landscape metaphor
The fitness landscape metaphor

Fitness

Selection

“Kind of”
The fitness landscape metaphor

Selection + randomness = reproduction

“Kind of”

Fitness

Number of offsprings

Selection + randomness = reproduction

“Kind of”
The fitness landscape metaphor

```
Fitness

Reproduction (with mutations)

"Kind of"
```
The fitness landscape metaphor
The fitness landscape metaphor

Fitness

Generation++

“Kind of”
The fitness landscape metaphor

Fitness

Generation++

“Kind of”
The fitness landscape metaphor

Fitness

Convergence ...

“Kind of”
Two antagonist forces

Fitness landscapes help ... but how to understand the metaphor?
Fitness landscapes help thinking

How to cross a valley?

What is the speed of evolution?

Why evolution does not use the shortest path?

What is the behavior of the population before the peak?

[Poelwijk et al. 2007]
Questions of fitness landscape

What is the shape of the landscape? Why?

Is the landscape static? If not, what triggers changes of the landscape shape?

What is the correct number of dimension?
Need for experimental evolutionary studies

• Evolution if a general mechanism that relies on many random events
  – How can we distinguish between the effect of the mechanism and the effect of the random events?
  – We only have a single “experiment” at our disposal!

• Many questions cannot be addressed without experiments (or only hardly addressed!)
  – Is there a trend in the evolution of biological complexity?
  – What if we start again?
  – Is evolution predictable?
  – Is evolution really universal? (Cf. Dennett)
  – What is true for E. coli is true for the elephant…
Experimental evolution

- Controlled experiments ARE possible for organisms which are
  - Cheep, small, abundant, controllable (organism and environment), fast (short generational time), measurable (sequence, fitness, ...), freezable ...
  - E.g., bacteria (*E. coli*, *salmonella*, ...), viruses and phages, yeast, *C. elegans*, *Drosophila*, ...

- Longest experiment in evolution
  - 12 strains of *E. coli* evolved during 40,000 generations in R. Lenski lab. at Michigan State University
  
  http://myxo.css.msu.edu/index.html
Experimental evolution is not enough

- All known organisms share parts of their evolutionary history
  - We all come from LUCA (~3.5 billion years ago)
- Conditions are always changed by the experimental setup
  - What are the consequences on the evolutionary process?
- How can we analyze the results?
  - Real organisms are too complex for us!

“So far, we have been able to study only one evolving system and we cannot wait for interstellar flight to provide us with a second. If we want to discover generalizations about evolving systems, we have to look at artificial ones.”

[John Maynard Smith, 1992]
Artificial life

- Life inside a computer?
  - Free forms ...

- Digital experiment on controlled organisms (artificial life)
Artificial Life in few steps

- 1978 First attempts (C. Langton, LANL)
  • “Life as it could be”
- 1990 Venus simulator (S. Rasmussen, LANL)
- 1991 Tierra (T. Ray, U. of Delaware)
- 1992 Creatures (K. Sims, digital corp.)
- 1993 Avida (C. Adami., C.T. Brown, C. Ofria, Caltech)
  • Probably the most classical digital genetic software today
- 1996 Amoeba (A. Pargellis, Lucent)
- 2000 Golem project (H. Lipson, J. B. Pollack, Brandeis Univ.)
  - 2005 Aevol (G. Beslon, C. Knibbe, INSA-Lyon)
- 2006 Evolving robots (D. Floreano, L. Keller, EPFL/UNIL)

• Note 1: Lots of researchers don’t use the term but construct models close to these ones (e.g., Paulien Hogeweg, Uri Alon, …)
• Note 2: Artificial life not only focuses on evolution but evolution is the heart of artificial life
QuickTime® and a decompressor are needed to see this picture.
Digital genetics

• Software that creates environment inside of a computer for populations of *self-replicating* elements, subject to *mutation* and *survival of the fittest*
  – “Real evolution of false organisms” (real Darwinism)

• This software can be used as an experimental setup
  – Modify some parameters of the simulation, look at the consequences on the organisms and/or on the ecosystem
  – Look for regularities…

• Experiments can be *repeated* many times for statistical accuracy.
  – All mutational events are known

• Digital Genetics = Agents-Based Modeling applied to evolution
Pseudo-code

“Creation”

$n$ genomes created randomly

“Selection”

Survival of the fittest …

Biased Random-wheel

“Evaluation”

Compute the fitness of each individual

“Reproduction”

Mutation and cross-over

Replacement strategies

The devil is in the details
Evolved Virtual Creatures (Karl Sims 1994)

- Each creature is defined by a graph
  - One node = one body element
  - One link = one joint
  - Dual-links = multiple bodies
  - Recursive links = repeated structures

- Nodes and links are valued
  - Dimensions
  - Joint limits
  - Relative position
  - Recursion control
  - Joint control
  - ...
Evolved Virtual Creatures
(Karl Sims 1994)

• Each creature owns a distributed brain that receives stimuli and produces motor output at the joints ...

• Example:
  – P1: body light-sensor
  – C0, P0, Q0: “wings” light-sensors
  – *, s+?: computation elements
  – E0, E1: joint motor control
Evolved Virtual Creatures
(Karl Sims 1994)

• Each creature “lives” in a precisely controlled world (viscosity, gravity, obstacles, light, …)
  – The emergent morphology and behavior is strongly dependent on the environment condition (although highly variable)

• The main difficulty is the computation of the fitness values (i.e. the simulation part!)
  – Each simulation error is rapidly detected and used by the creatures!

• Nice! What can we conclude?
  – Hmm … good question
  – It is almost impossible to disentangle the effect of evolution and environmental conditions from the effect of the (very complicated) genotype to phenotype mapping!
  – But Sims paved the way for many models (Framsticks, Golem….)
Too complex to comprehend?

• Creatures and similar models aim at simulating real “high level” organisms like mammals, birds, worms or snakes
  – The genotype-phenotype mapping is too complex
  – Interesting for engineering and computer graphics
  – Actually very few “real results” in evolutionary biology

• We need a more simple genotype-phenotype mapping
  – Models based on artificial chemistries

• Artificial chemistries
  – Computer instructions or sequences interpreted by a virtual CPU to produce the behavior of the organism
  – Historically artificial chemistries come from “core-war” games
  – Various formalisms [Dittrich et al., 2001] …
Tierra: the ancestor
(Tom Ray, 1992)

“In Tierra, the self-replicating entities are executable machine code programs, which do nothing more than make copies of themselves in the RAM memory of the computer. Thus the machine code becomes an analogue of the nucleic acid based genetic code of organic life”

[T. Ray]

• Tierra enables to study the evolutionary behavior of evolving entities engaged in an “open-ended evolution”
  − No goal but (implicitly) survive and reproduce
  − Need to be sowed by some predefined code able to self-reproduce

• Tierra is an evolving ecological system

[http://life.ou.edu/pubs/fatm/fatm.html]
Tierra: the ancestor
(Tom Ray, 1992)

• Evolution of host-parasite systems (time 1)
Tierra: the ancestor
(Tom Ray, 1992)

• Evolution of host-parasite systems (time 1)
Tierra: the ancestor
(Tom Ray, 1992)

• Evolution of host-parasite systems (time 1)
Tierra: the ancestor
(Tom Ray, 1992)

• Evolution of host-parasite systems (time 1)

Nice but …
Still we cannot conclude
Avida: the maturity
(Chris Adami, 1997)

• Avida is not only a “better” model; it also starts with better questions
  – Chris Adami interacts with biologists on an almost daily basis …
  – Important collaboration with Richard Lenski

• Avida uses a simpler artificial chemistry than Tierra
  – Each “avidian” contains its own CPU (no interaction during code execution)
  – Avidians are immersed in a 2D space
  – The evolution is no more open-ended (the “fitness” don’t have the same meaning!) but the results are easier to analyze!
  – Better trade-off between simplicity and complexity of the model

• Many results in biology
  – See e.g., C. Adami, T. Collier, S. F. Elena, C. Ofria, C. Wilke, R. Lenski, D. Misevic…
QuickTime® and a decompressor are needed to see this picture.

[Adami, 2006]
Experiments

- Two different organisms, same conditions
  - Yellow organism: good but not robust
  - Blue organism = not so good but robust

Mutation rate: 0.5

Mutation rate: 1.5
“Survival of the flattest”
Modeling the model

• “Survival of the flattest” [Wilke et al., Nature, 2001]
  - Under strong mutational pressure, sharp peaks are disadvantaged
  - When understood, the mechanism can be explained without the computational model ("the model is no longer needed afterwards")
  - E.g., interpretation in terms of fitness landscape … the yellow is “high and thin”, the blue is “low but flat”
The aevol/R-aevol model

An individual-based model of genome and regulation networks evolution and structuring


Origin of genomic structures?

**Homo sapiens**
- ~3 billions bp
- ~25 000 genes

**Neisseria meningitidis**
- ~2 millions bp
- ~2 000 genes

**Herpes HSV-1**
- ~150 000 bp
- ~100 genes

\[\text{Molina & Van Nimwegen, 2008}\]
Origin of genomic structures?

Genotype: variation (mutations)

Indirect selection for the appropriate level of variability

Phenotype: selection

Mutational biases:
“Homo Sapiens genome spontaneously undergoes more insertions than deletions”

Selective costs:
“A long genome can be disadvantageous for a bacteria or a virus”
Indirect selection
(a thought experiment)

Too frequent mutations:
- Lineage extinction → indirect selection for robustness

Favorable mutation

No mutation: Evolutionary dead end → indirect selection for variability

High variability level
(Low probability to reproduce neutrally: \( F_\nu \approx 0 \))

Mid variability level

Low variability level
(High probability to reproduce neutrally: \( F_\nu >> 1 \))

Organisms can be (indirectly) selected depending on their robustness and evolvability (i.e. depending on their ability to evolve; second-order selection)

... But what are (i) the relative influence of direct and indirect selection? (ii) the effect of indirect selection on genome architecture? (iii) the range of parameters in which indirect selection occurs? (and many others)
How to model indirect selection?

Genotype: variation (mutations)

Indirect selection

Phenotype: selection

Neutral models (simulation of real sequences evolution)

- Genome structure, mutational dynamic
- No phenotype, no selection

Population genetics avida

- Population, selection
- Genome structure, mutational dynamics
Contraintes sur le modèle

• Les structures moléculaires doivent être interprétables en termes biologiques
  – Génome, gènes, protéines, promoteurs, …

• Elles doivent être “évoluables”
  – Nombre de gènes variable, taille du génome variable, …

• Les structures moléculaires doivent être soumises à un processus mutationnel “réaliste”
  – Mutations ponctuelles
  – Remaniements chromosomiques
  – Transfert horizontal

• Les organismes ne doivent pas être sélectionnés en fonction de leur structure moléculaire
  – La sélection doit opérer sur le phénotype
The aevol model

Genome
- 10,756 bp
- 80% non-coding
- 43 genes

20000 generations

Replication (mutations, rearrangements)

Population

Selection

Phenotype

Environment

Genome
- 5,000 bp
- 98% non-coding
- 2 genes

Genome
- 10,756 bp
- 80% non-coding
- 43 genes

Proteome

Biological process

Phenotype

Possibility degree

Effect

Biological process

Possibility degree
Transcription in aevol

<table>
<thead>
<tr>
<th>Promoter sequence</th>
<th>Transcribed region</th>
<th>Terminator sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>...110...010...0110111010001011100111011011010001...10110010010...</td>
<td>...001...101...100100010111010001100011000100101110...01001101101...</td>
<td>...01001101101...</td>
</tr>
</tbody>
</table>

Comparison

Expression level $e$

Consensus $100...010$
Translation in aevol

Coding sequence (gene)

\[ \ldots 110...010...011011101000101110011100111011100001...10110010010... \]

\[ \ldots 001...101...100100010110.00011100.10001000.011110.00100111010010...1001101101101... \]

Genetic code

<table>
<thead>
<tr>
<th>Code</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>000</td>
<td>START</td>
</tr>
<tr>
<td>001</td>
<td>STOP</td>
</tr>
<tr>
<td>100</td>
<td>M₀</td>
</tr>
<tr>
<td>101</td>
<td>M₁</td>
</tr>
<tr>
<td>010</td>
<td>W₀</td>
</tr>
<tr>
<td>011</td>
<td>W₁</td>
</tr>
<tr>
<td>110</td>
<td>H₀</td>
</tr>
<tr>
<td>111</td>
<td>H₁</td>
</tr>
</tbody>
</table>

« start » signal

« stop » signal

Conversion to integer and normalization

\[ m = 0.86 \quad w = 0.02 \quad H = 0.33 \]

Real value

0.86

0.02

0.33
Protein-protein interactions

- Interactions by triangles overlap
  - Pleiotropy
  - Polygeny

- Fuzzy sets combination
  - Phenotype = set of activated functions minus set of inhibited functions
  - Lukasiewicz operators
  \[ P = (\bigcup A_i) \cap (\bigcup I_j). \]
- Punctual mutations
- Small insertions
- Small deletions
- Translocations
- Inversions
- Duplications
- Large deletions

In mean, $\mu L$ per reproduction

$\mathcal{Æ}vol$: Reproduction cycle

$N$ individuals

Random or clonal initialization

Reproduction mutational process

Phenotype computation

Comparison with environmental reference

Computation of $W$ (number of offspring)

$W \approx N \cdot \text{prob}(\text{reproduction})$
Ævol: The movie (« winning » lineage)

Genome length = 25993 bp
Small insertion at 19406 of sequence 01
**In-silico experimental evolution**

- Mutation rate $u$:
  - Six mutation rates from $u = 5 \times 10^{-6}$ to $u = 2 \times 10^{-4}$ per bp
  - Same mutation rates for point mutations and rearrangements
- Selection:
  - Two selection modes (fitness proportional or rank-based)
  - Different selection strength (here $k = 250$ or $k = 1000$)
- Experimental evolution during 20000 generations
  - Populations: 1000 individuals
  - Steady environment
- Three repetitions per couple $(u,k)$
  - More than 100 simulations
  - It’s *really* an experimental approach …
Ævol: The movie (II) ...

High mutation rates : $2 \times 10^4$ / pb

Low mutation rates : $5 \times 10^{-6}$ / pb
Scaling laws emerge *in silico*

\[ u = 5.10^{-6} \]

- ~ 50000 bp
- ~ 60 genes
- ~ 95% non-coding

\[ u = 2.10^{-1} \]

- ~ 500 bp
- ~ 10 genes
- ~ 15% nc

**Buchnera aphidicola**

**Papillomavirus**
Yet another model explaining everything ;)!

The model is able to reproduce known (but unexplained) data …

But “Prédire n’est pas expliquer” (R. Thom) …
Experiments in the model

The Regulation of the number of neutral offspring is the hallmark of an indirect selection process; the link between the mutation rate $u$ and the size of the non-coding sequences show that the indirect selection depends (at least partly) on these sequences…

… But what is the link? Where does the burden come from?
Mathematical model of reproduction

- The math model represents aevol AND the "real world"...

\[ F_i : \text{Probability of neutral reproduction as a function of genome size, } (L), \text{ mutation rate } (u) \text{ and neutrality of each kind } i \text{ of mutation } (\nu_i): \]

\[ \forall \nu_i : \tilde{\nu}_i : \text{Probability for a mutation of type } i \text{ to be neutral depending on the genome structure:} \]

If: (i) genomes undergo large duplications and deletions, (ii) the number and the average size of these events increase with genome size, Then: the mutational variability of a lineage depends on the amount of non-coding DNA (it is mutagenic for the genes it surrounds).

Thus the indirect selection for an appropriate level of variability actually selects for a specific amount of non-coding DNA

\[
\begin{align*}
\tilde{\nu}_{\text{pont}} &= \tilde{\nu}_{\text{ins}} = \tilde{\nu}_{\text{del}} = 1 - \frac{l}{L} \\
\tilde{\nu}_{\text{inv}} &= \left(1 - \frac{l}{L}\right)^2 \\
\tilde{\nu}_{\text{transloc}} &= \left(1 - \frac{l}{L}\right)^3 \\
\end{align*}
\]

\[
\begin{align*}
\tilde{\nu}_{\text{gdel}} &= \frac{1}{2L^2} \sum_{j=1}^{N_G} \lambda_j \left(\lambda_j + 1\right) \\
\tilde{\nu}_{\text{dup}} &= \frac{1}{2L^2} \left(1 - \frac{l}{L}\right) \sum_{j=1}^{N_G} \lambda_j \left(\lambda_j + 1\right)
\end{align*}
\]
Care natural interpretations ;)

« It is simply a truism that the observed genome size is the result of a balance between the rate of DNA gain and loss » (Gregory, 2004)

DNA gain: duplications
DNA loss: deletions

\[ \mu_{del} \]

\[ L_2 < L \]

\[ \mu_{del} = \mu_{dil} \]

\[ \mu_{dil} = \text{Cst.} \]
Care natural interpretations ;) 

• Metabolic error ~ inverse of the fitness value
  – After generation 20 000, the metabolic error increases!
• Evolution DECREASES the fitness ! (how is it possible?)

\[ F \nu W \approx 1 \]
What about gene networks?

[Diagram showing the number of genetic domains per functional category for different organisms.]

G. Beslon – Ecole de Porquerolles – 11 juin 2010
Contraintes sur le modèle

• L’évolution des réseaux de gènes est un “hot-topic”
  – Voir les travaux de W. Banzhaf, D. Floreano, P. Hogeweg, U. Alon, J. Knabe …

• Pourquoi un modèle de plus sur la base de aevol ?
  – Un modèle de l’évolution des réseaux de régulation est d’abord un modèle de l’évolution !

• Les contraintes posées pour aevol sont toujours valides !
  – C’est le génome qui mute
  – C’est le phénotype qui évolue
  – Le réseau est “entre les deux” : il évolue indirectement !

• Contraintes supplémentaires :
  – Le réseau évolue en CIS et en TRANS …
  – Pas de mutation directe des liens !
  – Attention : ici la différence procaryotes/eucaryotes est fondamentale !
In R-aevol, the organisms own a genome and a regulation network. The network is made of metabolic genes and transcription factors ...

Experiments in R-aevol: How does the network structure depend on the evolutionary conditions? (e.g., environment complexity)
R-aevol: introducing regulation into aevol

Equations de Hill

Taux de transcription final de la protéine
R-aevol: introducing regulation into aevol
R-aevol: regulation in aevol

- In R-aevol, the organism’s phenotype becomes a function of time
  - Organisms have a “life”; they can interact with their environment
  - Experiments in a two-states environment; the metabolic error is computed at $t = 10$ and $t = 20$
Evolved network after 15000 generations

How can we understand such a (complex) net?
Systematic Knock-Out experiments

Wild Type

KO Gène 1

KO Gène 2

KO Gène 3

KO Gène 4

KO Gène 5

KO Gène 6

KO Gène 7

KO Gène 31

KO Gène 32

KO Gène 33

Clustering...
Reduced “schematic” network with two modules
Origin of complexity

• Where does the network complexity come from?
  – [In less stable, more changing environments, transcription factors are over-represented] ... This suggests that in ever-changing, highly competitive environments, there is a strong selective pressure towards regulated and coordinated gene expression, compared with very stable environments. (Cases et al., 2003)

• According to this view, the origin of (transcriptomic) complexity is another (environmental) complexity!
  – But in our experiments, the complex network emerged in a simple environment (two states)

• What about the effect of the mutation rate?
  – Similar experimental protocol as in aevol …
  – Six mutation rates, three repetitions, 40 000 generations
Impact of mutation rates on genomic structures

- The mutation rate is a major determinant of genome size and gene number.

[Graph showing the relationship between mutation rate and genomic structures.]

[Beslon et al., IPCAT'09]
Impact of mutation rates on transcriptomic structures

$\mu = 5 \times 10^6$

$\mu = 5 \times 10^5$

$\mu = 2 \times 10^4$

[Beslon et al., IPCAT’09]
[Beslon et al., BioSystems 2010]
R-aevol: emergence of scaling laws (1)

Domains in genome

Biological data
(Molina & Van Nimwegen, 2008)

Genes with regulative activity (circles - log scale)
Genes with metabolic activity (squares - log scale)

Total number of genes

Domains in functional category

Domains in genome

metabolism
translation
regulation

slope = 0.883
R-squared = 0.975

slope = 1.47
R-squared = 0.893
R-aevol: emergence of scaling laws (2)

Complexity emerges “for free” (environmental complexity is NOT a necessary condition)

Can indirect selection explain this result?
In R-aevol, the structure of the genetic networks seems to be indirectly selected to regulate the mutational variability of the organisms \( (F_v \ W = 1) \).

A new analysis paradigm for genetic networks understanding?

... To be continued
Evolutionary systems biology
- Provides essential clues to understand biological systems
- But models are necessary

Digital genetics
- Opens a new window on evolution
- Enables experimental studies in evolution
- "Survival of the flattest"
- Indirect selection of genetic structures (robustness/evolvability)

Evolutionary history can explain the genomic diversity
- Emergence of a new paradigm in systems biology? (complexity first)
- What is the environment of an organism?

Take-Home Message
QuickTime® et un décodeur de décodeur de comporte un compresseur sont requis pour visionner cette image.
C’est l’interdisciplinarité qui nous permet de conclure, pas le modèle

« Dans les champs de l’observation, le hasard ne favorise que les esprits préparés » (Louis Pasteur)