



agence d'évaluation de la recherche  
et de l'enseignement supérieur

Department for the evaluation of  
research units

AERES report on interdisciplinary unit:

Institut de Biologie Systémique et Synthétique

ISSB

Under the supervision of the following  
institutions and research bodies:

Université d'Evry-Val-d'Essonne - UEVE

Centre National de la Recherche Scientifique - CNRS

February 2014



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et de l'enseignement supérieur

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*On behalf of AERES, pursuant to the Decree  
of 3 november 2006<sup>1</sup>,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation  
of research units department

*On behalf of the expert committee,*

- Mr. Jean-Luc GALZI, chair of the  
committee

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<sup>1</sup> The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n° 2006-1334 of 3 November 2006, as amended).



## Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

|  |  |
|--|--|
| Unit name:                             | Institut de Biologie Systématique et Synthétique |
| Unit acronym:                          | ISSB   |
| Label requested:                       | UMR CNRS   |
| Present no.:                           | FRE 3561   |
| Name of Director<br>(2013-2014):       | Mr Jean-Loup FAULON                              |
| Name of Project Leader<br>(2015-2019): | Mr Jean-Loup FAULON                              |

## Expert committee members

Chair: Mr Jean-Luc GALZI, University of Strasbourg

Experts: Mr Daniel KAHN, INRA, Lyon (representative of CoNRS)  
Mr Marc MOREAU, CNRS, University of Toulouse  
Mr Wilfried WEBER, University of Freiburg, Germany

Scientific delegate representing the AERES:

Mr Jacques HAIECH

Representative(s) of the unit's supervising institutions and bodies:

Mr Michel GUILLARD, University Evry-Val-d'Essonne  
Mr Francis QUETIER, Genopole  
Mr Bernard MIGNOTTES (Head of doctoral school n° 423)  
Mr Bruno MIROUX, INSB CNRS



## 1 • Introduction

### History and geographical location of the unit

The project leading to the creation of the « Institute of Systems and Synthetic Biology » ISSB started early 2000 with the Epigenomics program of the Evry Genopole (1999). Three teams (teams 1, 2 and 4) joined the founding team (n° 3) between 2006 and 2008 to become a « unité propre de service UPS 3201 », before becoming recognized as a FRE in 2013. In 2011 an additional team (n° 5) joined to build the laboratory as it is presently.

The unit gathers 44 persons, out of which 16 are permanent researchers (7 CNRS), professors or associate professors (8), engineer (1) and technicians (2). Non permanent researchers are PhD students (12), Post docs (9) technicians and engineers (7).

The unit also manages two technological platforms, i) abSYNTH, for design, construction and characterization of synthetic systems and ii) CERFAP for animal experimentation, shared with a private company.

The unit is located in two buildings at genopole campus 1. Teams 1,2,3 and 5 are grouped in one building from the genopole campus and Team 4 is in a neighbouring building equipped for Xenopus farming and experimentation purposes. The whole laboratory will be grouped in another building (Genoscope) in 2015.

### Management team

The laboratory is headed by Mr Jean-Loup FAULON, professor at Evry-Val-d'Essonne University.

He is assisted by a deputy director, an executive committee, a laboratory council and a Scientific Advisory Board recently created gathers 6 international high level personalities.

### AERES nomenclature

SVE1\_LS1, SVE1\_LS2, SVE1\_LS3 , SVE2\_LS9, ST4, ST5, ST6.

### Unit workforce

| Unit workforce   | Number as at 30/06/2013 | Number as at 01/01/2015 |
|--|-------------------------|-------------------------|
| <b>N1:</b> Permanent professors and similar positions  | 6                       | 7                       |
| <b>N2:</b> Permanent researchers from Institutions and similar positions   | 6                       | 6 (+1)                  |
| <b>N3:</b> Other permanent staff (without research duties)   | 3 (2,8)                 | 3 (2,8)                 |
| <b>N4:</b> Other professors (Emeritus Professor, on-contract Professor, etc.)                                      |                         |                         |
| <b>N5:</b> Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.) | 12                      | 11                      |
| <b>N6:</b> Other contractual staff (without research duties)   | 7                       | 7                       |
| <b>TOTAL N1 to N6</b>  | <b>34</b>               | <b>34</b>               |



| Unit workforce   | Number as at 30/06/2013 | Number as at 01/01/2015 |
|--|-------------------------|-------------------------|
| Doctoral students  | 11                      |                         |
| Theses defended  | 5                       |                         |
| Postdoctoral students having spent at least 12 months in the unit* | 7                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken           | 1                       |                         |
| Qualified research supervisors (with an HDR) or similar positions  | 7                       | 9                       |

## 2 • Overall assessment of the interdisciplinary unit

The research done by the unit is situated in a rapidly evolving and very innovative field.

The quality of the scientific production is globally very good both in basic and applied science (see for detailed assessments on the production).

ISSB is a young research unit that has established itself during the past contract period. The marked organization efforts carried out by the director to structure the strategy of the laboratory deserve to be emphasized.

### Strengths and opportunities related to the context

ISSB is one of the largest synthetic biology laboratories in France. It has acquired notoriety and is recognized as one of the leading groups at the national level. It has in particular integrated researchers with international reputation who develop very innovative and ambitious projects.

The laboratory is notoriously attractive to young and enthusiastic graduate and post-doctoral scientists. It has succeeded in establishing innovative partnerships with companies and foreign researchers to extend its field of competence.

ISSB is actively involved in technology development and transfer, through implementation of transdisciplinary platforms as well as by participating to start up companies in which laboratory members are either officers or founders. Overall, there are excellent opportunities for translational science.

Almost all members of the laboratory are involved in teaching at the graduate and post graduate levels. They created a Master in systems and synthetic biology and are mentors of groups of PhD fellows who participate to the international competition on genetically engineered machines (iGEM) at which their teams were awarded up to the gold medal level.

The director has managed to deploy a common strategy integrating all groups and their respective expertise in a coherent project spanning all levels of organization of the living. This global project encompasses all required disciplines for projects in integrated synthetic biology to be successful.

The relocation of the laboratory, planned for the term to come, is an opportunity for ISSB to improve its capacities, by gathering all teams in a single building, gaining additional lab space to accommodate a new team in cell biology, and very importantly, establishing sustained cooperation with groups working in metabolomics through sharing of high performance analytical equipments, skills and technical personnel.



### Weaknesses and threats related to the context

ISSB is exposed to a threat concerning its management organization. Indeed, several teams are led by principal investigators who are involved in several demanding projects such as intensive teaching, or are bi-localized, or should retire by the end of the next contract period. There is thus a real concern about risks of management vacancy since the laboratory does not have a large number of permanent staff to take over team leadership. Another laboratory organization might be more adapted to the rapidly evolving configuration of the teams.

In addition there is no consortium agreement, yet, with the company Isthmus with which ISSB is collaborating.

### Recommendations

Collaborations with companies involved in ISSB management or projects should be formally contractualized.

In its future strategy, the laboratory should consider an organization comprised of a single team with multiple research themes that may turn to be well adapted to forthcoming uncertainties regarding team management especially for teams 2 and 5. Inter-theme technical collaborations with scientists dedicated to projects rather than to groups may be useful to allow flexibility and efficient internal communication, in terms of both research and management.

The management team should also worry about establishing consortium agreements with the companies with which they already collaborate and the one that they plan to establish in a near future

Advantage should be taken from the relocation of the unit within the genopole buildings to share analytical resources, skills and technical personnel with the other UMR.



### 3 • Detailed assessments

#### Assessment of scientific quality and outputs

Globally during the past five years the laboratory published 97 peer reviewed articles in specialized (NAR, Bioinformatics J., J Comp. Chem., Biotech J., Biophys J., ...) but also in broad audience journals (such as Angew. Chem, PNAS, Genome Biol. ... ) as implementing body or as co-investigators (Nat biotech, Science). ISSB members also contributed 29 books and chapters. More than half of the published articles and reviews are issued from the laboratory as can be judged from authorship analysis (first or last author).

Laboratory members gave 56 invited conferences at national or international congresses and gave another 50 talks/seminars in research institutes. Research themes are globally original (metabolic engineering, XNA engineering, genome engineering, regulatory circuits with RNAs ).

Some groups are clearly leaders in their field at the international level. Yet, the team by team analysis (below) shows heterogeneity in the average number and quality of publications.

ISSB has released 10 software products that are usable by the scientific community.

The laboratory is clearly a leader in the field of synthetic biology.

#### Assessment of the unit's academic reputation and appeal

Some indicators of the laboratory reputation are detailed above, such as the number of invited lectures at international conferences and research centers, but an important factor is the capacity to raise funding for research which is to be considered very high.

It is easy indeed to notice that ISSB is very attractive to young scientists, as they represent most of the personnel of the laboratory. The reputation of the laboratory, as can be appreciated from the proportion of foreign post doctoral fellows, is undoubtedly international.

ISSB succeeded in attracting a renowned researcher to lead the xenome team. It is also an active member of the ERA NET Synbio. It is also involved in the establishment of a national network (GDR) on synthetic biology, at the request of the Centre National de la Recherche Scientifique.

#### Assessment of the unit's interaction with the social, economic and cultural environment

ISSB has globally important connections with social, economic and cultural environment.

During the past 5 years the laboratory obtained 9 M€ of grants. The academic grants were obtained mostly from international calls (7 european grants, 1 ERC grant). Members of the laboratory are often principal investigators of collaborative studies.

Teams from the ISSB undertake outreach actions to popularize their research through books for general public, television programs (ARTE) or newspapers (Le monde, Le Figaro). They also contribute to the Wikipedia page on xenobiology.

Through the participation to the international iGEM competition, ISSB-coached teams received awards such as a gold medal for "Best model" and "Best Human Practice".

ISSB has long lasting collaboration with the Société à Responsabilité Limitée (SARL) Isthmus, with employees of the company working in the laboratory. They are also founding members of the company Abolis to be launched in 2014.



### Assessment of the unit's organization and life

The laboratory director is assisted by a board of team leaders (monthly meeting) and a laboratory council (3 per year). He has recently finalized the external Scientific Advisory Board that will be in charge of selecting a new team specialized in cell biology. Invited speakers present their work at least once a month. This scientific animation is coupled to that of the Master in systems and synthetic biology.

It appears quite evident that the members of the laboratory are happy to work in the laboratory and to take advantage of the dynamic management which provides support in the form of multiple successful European initiatives.

Students and post docs all participate to an international scientific meeting at least once a year. Thesis Committees are held once a year

The current head of the laboratory has been chosen to continue his function for the term to come. He is appreciated by colleagues, technicians and students.

### Assessment of the unit's involvement in training through research

ISSB attracts an impressive number of doctoral and post-doctoral fellows (all coming from abroad). 6 PhD theses were defended since 2010, and a very fair number (11) of PhD fellows are present in the laboratory. Doctoral fellow are registered in the doctoral school entitled "Des Génomes Aux organismes" (ED 423).

Researcher and professors have set up and lead a master course in systems and synthetic biology that gathers more than 20 students each year since 2010. They manage several modules from this training course.

They also organized one international conference on synthetic biology in 2010.

ISSB is in the process of identifying the members of the national community in synthetic biology to launch and lead a groupement de recherche (GDR) in 2015.

### Assessment of the strategy and the five-year plan

After having supported each team to set up its own activity in the new laboratory and to develop individually during the past contract period, the management team has set up a common strategy. The new strategic program comes into three main lines of activity : Research, Technology transfer and Education.

The research axis encompasses different levels of organization of the living, namely metabolism at the cell level (team 1), Regulation of gene expression (team 2), organization of genes in the genome (team 3), integration at the animal level (team 4) and finally the exploration of artificial genetic encoding of information (team 5). Operationally, each level is treated according to a three step process that starts with the design of new items, followed by construction and characterization. The AbSynth platform provides the technical tools common to all themes. Design relies on extensive modelling using a set of ten internally-developed softwares and high performance computing.

Construction uses standard molecular biology tools operated with high throughput robots that parallel production of desired genetic networks and their variants obtained with different orthologs, paralogs, mutants, gene expression control systems ....

Characterization is achieved using a set of PCR, microscopes, microfluidics, purification, mass spectrometers and the frog animal facility. The three steps, design, construction and characterization are operated using an iterative process for improvement based on learning.

The technology transfer axis comprises several items. One of them is the close collaboration with the company Isthmus, specially involved in the xenome project. Another is the forthcoming creation of the start up company Abolis in which members of the laboratory are founders. Other aspects are public-private partnerships on the abSYNTH technological platform.

The Education project comprises the animation of a Master program in Systems and Synthetic Biology (MSSB) at the University of Evry-Val-d'Essonne, deep involvement in the animation of the doctoral school through the participation to the yearly iGEM competition with implication of doctoral students to support graduate student teams.





To support the development of the research program, the laboratory will move to another building in the genopole to be closer to another laboratory that has expertise in metabolites analyses, but also to gain more space to harbor all exiting teams in a single place and accommodate an additional group with competence in the eukaryotic cell field, as this is lacking for complete coverage of organization levels.

Altogether the strategy of the laboratory for the five next years is admirably conceptualized. Its implementation does seem clear-cut as all team leaders have adopted it in all the projects. The laboratory is strongly supported by the genopole for the laboratory reorganization, by the doctoral school for the doctoral program and by the university Paris Saclay for the MSSB Master program.



## 4 • Team-by-team analysis

**Team 1 :** BIO-RETROSYNTH

Name of team leader: Mr Jean-Loup FAULON

Workforce

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| <b>N1:</b> Permanent professors and similar positions                                   | 2                       | 2                       |
| <b>N2:</b> Permanent EPST or EPIC researchers and similar positions                     |                         |                         |
| <b>N3:</b> Other permanent staff (without research duties)                              |                         |                         |
| <b>N4:</b> Other professors (PREM, ECC, etc.)   |                         |                         |
| <b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) | 3                       | 3                       |
| <b>N6:</b> Other contractual staff (without research duties)                            |                         |                         |
| <b>TOTAL N1 to N6</b>   | <b>5</b>                | <b>5</b>                |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   | 3                       |                         |
| Theses defended   |                         |                         |
| Postdoctoral students having spent at least 12 months in the unit | 1                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken          | 1                       |                         |
| Qualified research supervisors (with an HDR) or similar positions | 2                       | 2                       |



## • Detailed assessments

### Assessment of scientific quality and outputs

The team is led by the director of the laboratory who is in addition full professor at the university Evry Val-d'Essonne. Considering these two major investments in research and teaching, and taking into account the moderate size of the group, the production of the team is good (22 articles). Although the papers appear essentially in specialized journal (J Chem Inf Model, BMC Systems Biol., JBC, Biotechnology and bioengineering, ...), the leadership of the team is obvious in more than 80% of them. Several book chapters (5) have also been contributed in the "Handbook of ..." and "Methods in ..." series, in addition to a Handbook of Chemoinformatics that was fully edited by the team leader. Four softwares (Promis, EcoTox, Scan, Retropath) and two additional ones were released on sourceforge. One patent was filed in 2012.

Sixteen conferences were given at the international level in symposia and institutes and another 15 were given in French scientific meetings.

### Assessment of the unit's academic reputation and appeal

As can be judged from the number of foreign post-doctoral fellows, the group has excellent visibility abroad. As mentioned above, members of the group are invited to international meetings, they organize or chair symposia on bioinformatics (2008) synthetic biology (2010) and Biomanufacturing (2010). Finally, the team leader is visiting faculty at UCLA.

### Assessment of the unit's interaction with the social, economic and cultural environment

The team is highly successful in obtaining research grants at the national (ANR, Genopole, CNRS, DGA, AXA, Université PSud) european (FP7 IST FET, FP7 KBBE) and international (US DOE programs) levels.

The team leader is also involved in a start-up company (Abolis), that will exploit know-how and patents from the group.

Contracts with private companies are ongoing in the field of metabolic engineering for producing chemicals of commercial importance.

Finally representatives of the team participate to public debates and radio transmitted scientific debates and presentations.

### Assessment of the unit's organization and life

Not applicable

### Assessment of the unit's involvement in training through research

Clearly, the team leader plays a key role in setting up new formations and training in synthetic and systems biology and in supporting young scientists to participate to the international iGEM contest. This implication in training is discussed in the whole laboratory evaluation part.

### Assessment of the strategy and the five-year plan

There is a clear project that makes use of the assets of the team in the field of metabolic pathways engineering for the production of new chemical molecules of physiological, therapeutic and commercial interest. The laboratory is pursuing software and instrumentation developments in order to i) robotize plasmid design and LC-MS analyses and ii) optimize expression assays to generate pathways diversity and thus gain access to new molecules to produce.

An original aspect of the project is the idea to generate new pathways to convert compounds of interest into genetic effectors, thus giving access to the development of new biosensors.



In order to have access to large scale molecule production, the synthetic enzymatic pathways will be transferred to yeast.

## Conclusion

### ▪ Strengths and opportunities:

- The team benefits from a high level of expertise in his field and from support provided by the Genopole and University of Evry.
- It has a leading position in France in the field of metabolic pathways engineering and more generally in synthetic biology.

### ▪ Weaknesses and threats:

- Although the group has a leading position in his research domain at the national level, the field is very competitive at the international level.
- The multiple commitments of the team leader are impediments to an extended development of the activity.
- There is only limited expertise in the group in analytical sciences, especially in biological mass spectrometry and metabolomics

### ▪ Recommendations:

- The group should rely more heavily on the expertise of neighboring units in analytical science issues through collaborations and possibly through setting up common instrumental resources and platforms.



**Team 2 :** SYNTH-BIO

Name of team leader: Mr Alfonso JARAMILLO

Workforce

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| <b>N1:</b> Permanent professors and similar positions                                   | 1                       | 1                       |
| <b>N2:</b> Permanent EPST or EPIC researchers and similar positions                     | 1                       | 1                       |
| <b>N3:</b> Other permanent staff (without research duties)                              |                         |                         |
| <b>N4:</b> Other professors (PREM, ECC, etc.)   |                         |                         |
| <b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) | 2                       | 2 (+5)                  |
| <b>N6:</b> Other contractual staff (without research duties)                            | 2                       | 2                       |
| <b>TOTAL N1 to N6</b>   | <b>6</b>                | <b>6</b>                |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   | 4                       |                         |
| Theses defended   | 3                       |                         |
| Postdoctoral students having spent at least 12 months in the unit | 2                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken          |                         |                         |
| Qualified research supervisors (with an HDR) or similar positions | 1                       | 1                       |



## • Detailed assessments

### Assessment of scientific quality and outputs

In the past 5 years, the group Synth-Bio has established a highly innovative research field aiming at designing, constructing and applying RNA-based switches to control and fine-tune signaling and metabolic processes in bacteria. This research is based on a perfect combination of three disciplines that are rarely found at this high level of expertise within one single research group: (1) high competency in the development of mathematical models and algorithms to modeling and predict functional RNA secondary structures (2) a state-of-the-art wet lab for implementing the computer-designed tools in bacteria and (3) the tools and the competency to design and manufacture microfluidic devices for the multiparallel characterization and optimization of genetic networks in individual cells or small cell populations. The latter two elements were initiated to be implemented in 2008 and were rendered functional within a short time frame. Thanks to this combination it was possible to design and functionally validate novel RNA-based regulatory elements that function as molecular AND gate or that emulate a two-component signal transduction mechanism. The combination by input and output elements on one single RNA molecule enabled the design and implementation of a “molecular relais” (termed regazyme) that perceived an external signal and transmits this signal in a predefined manner to control the biosynthesis of an output protein. The robustness and stability of such RNA-based switches was increased by the highly innovative construction of a regulating circular RNA molecule in the cell.

The potential of combining the three elements (modelling, wet-lab, microfluidics) is documented by a continuous increase in the quality and quantity of scientific publications, for example two papers in PNAS and one paper in Nucleic Acids Research were published with the Synth-Bio group leader as last author. Given the so-far unpublished data, it is highly likely that the quality and quantity of the publication output will further increase.

The work by the Synth-Bio is perfectly aligned with the overall strategy of iSSB as it allows the control and fine-tuning of synthetic biology-based production processes. The tools having been developed and validated to date can directly be integrated into joint projects of the different groups of the unit for realizing the synergies by their complementing expertises.

### Assessment of the unit's academic reputation and appeal

The groups Synth-Bio has high international visibility and reputation which is based on the following points:

The group leader of Synth-Bio is one out of two French researchers that are highlighted on the scientific synthetic biology landscape in a recent survey published in PLoS ONE (Oldham et al., 2012, Synthetic Biology: Mapping the Scientific Landscape, PLoS ONE 7(4): e34368. doi:10.1371/journal.pone.0034368, see Figure 7 there).

The Synth-Bio group is/was involved in 4 FP7 and 1 FP6 research project where the Synth-Bio group is currently the coordinator of 1 FP7 project.

The Synth-Bio group has established computational tools for the automated design of biological pathways. These programs are available to the scientific community via internet.

The leader of the Synth-Bio group is member of the editorial board of ACS Synthetic Biology and of J Biol Eng.

The leader of the Synth-Bio group has recently been appointed as Full Professor in Warwick while still maintaining his research group at iSSB.

The leader of the Synth-Bio group was organizer of a synthetic biology conference at Evry and he has also attended key conferences in the field like the Gordon conference on synthetic biology in 2013.

The Synth-Bio group regularly attracts postdocs from abroad. The high quality of these postdocs is shown by the fact that two of them obtained group leader positions in France and Spain in 2014.



### Assessment of the unit's interaction with the social, economic and cultural environment

The Synth-Bio group is actively involved in transferring its expertise in synthetic biology to the social and cultural environment. For example, the leader of the Synth-Bio group is advisor to the Assemblée Nationale, to the Direction Générale de l'Armement and to the French Academy of Engineering. He was furthermore advisor of two Evry iGEM teams (2012 and 2013) where one important task is the analysis of the societal and ethical impacts of synthetic biology. For example, in 2013 the Evry iGEM team won the award for the best Human Practice Advance (category postgraduates).

Transfer of methods/patents to the economical sector has so far not been realized, however, based on the tools currently being developed by Synth-Bio, such transfer activities are likely within the next 5 years.

### Assessment of the unit's organization and life

The Synth-Bio group is excellently integrated into the unit's organization and everyday life, on both, the technological and scientific level. Please see the general description on the organization of the unit.

### Assessment of the unit's involvement in training through research

The Synth-Bio group is perfectly aligned with the training activities of the unit. The Synth-Bio group organizes the Synthetic Biology module in the mSSB curriculum and was also involved in the Evry iGEM teams in 2012 and 2013. Let consult the general description on the teaching.

### Assessment of the strategy and the five-year plan

The future strategy of the Synth-Bio group is perfectly in line with the overall strategy of the unit. The five-year plan is designed to harvest the fruits of the expertise, tools and technologies developed in the past five years while in parallel pursuing novel avenues for sustaining the scientific output.

The tools developed so far by the Synth-Bio group are now ready for application in joint projects of the unit, for example at the interface with the groups Bioretrosynth or Metamorphosis. Joint grant applications have been submitted or are in preparation.

As future avenues, the Synth-Bio group aims at realizing value of its unique combination in expertise and technology (modelling, wet-lab, microfluidics) by developing a whole set of broadly applicable RNA-based tools such as (cooperative) activators, signal transduction cascades, RNA-based fluorescent output devices, transcriptional repressor or time delay circuits. These functionalities have so far not been realized on an RNA level and will very likely generate significant impact in the synthetic biology community and beyond. These tools can directly be transferred to application within the unit but also within the different national and international projects in which the Synth-Bio group is involved as partner or coordinator.

In order to further sustain the technological advance and scientific productivity, the Synth-Bio group will integrate a new technology platform within the next five years in the frame of the Evoprog and Promys FP7 networks: It will use computationally-directed evolution to identify and optimize RNA-based switches with functionalities or performance characteristics not well addressable with today's technology.

Based on the group's past achievements and interdisciplinary collaboration in different local, national and international networks, it is likely that these ambitious plans will successfully be implemented.

### Conclusion

With the recent integration of modeling, wet-lab and microfluidics, the scientific productivity and reputation of the Synth-Bio group has continuously increased and is now recognized as player in the global synthetic biology landscape. The group is very well positioned to further increase its scientific output with regard to quality and quantity. Based on such increase, the group might achieve a position among the leading synthetic biology groups worldwide. The future strategy of the group is in alignment with these aims.



▪ **Strengths and opportunities:**

- Complementing expertise and technologies rarely present within one single research group;
- State-of-the-art equipment available;
- Well integrated into local, national and international research networks.

▪ **Weaknesses and threats:**

Multiple appointments of the leader of the Synth-Bio group (Full professor in Warwick, subgroup in Valencia). This multi-locus affiliation with different administrative and organizational backgrounds as well as the frequent travel might impact the availability of the group leader for the team members in the different labs. Also, having in parallel the possibility for several full positions increases the risk that the group might quickly leave one location upon a decrease in local conditions.

▪ **Recommendations:**

The group is very well on track. In order to continue its success story it is recommended to (i) ensure that the inherent drawbacks of the multi-locality do not compromise research and (ii) that the present and future technologies and tools developed by this group will be translated towards applications locally or with outside world-class partner in order to realize their full scientific, technological and also economical potential.





**Team 3 :** MEGA

Name of team leader: Mr François KEPES

Workforce

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| <b>N1:</b> Permanent professors and similar positions                                   | 1                       | 1                       |
| <b>N2:</b> Permanent EPST or EPIC researchers and similar positions                     | 2                       | 2                       |
| <b>N3:</b> Other permanent staff (without research duties)                              |                         |                         |
| <b>N4:</b> Other professors (PREM, ECC, etc.)   |                         |                         |
| <b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) | 4                       | 4                       |
| <b>N6:</b> Other contractual staff (without research duties)                            | 2                       | 2                       |
| <b>TOTAL N1 to N6</b>   | <b>9</b>                | <b>9</b>                |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   | 2                       |                         |
| Theses defended   | 2                       |                         |
| Postdoctoral students having spent at least 12 months in the unit | 4                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken          |                         |                         |
| Qualified research supervisors (with an HDR) or similar positions | 2                       | 2                       |



## • Detailed assessments

### Assessment of scientific quality and outputs

The team is composed of 3 permanent and 6 non-permanent scientists.

The aims of the team is to model the Genome Architecture and from this knowledge, to be able to engineer artificial chromosomes.

The rationale behind this work is the working hypothesis that the genome topology also controls gene expression and modulation of transcriptome factors' regulation.

The team has proposed the solenoidal model of chromosomes and the consequences of such model on the transcriptional modulation of genes, first in bacteria and now in eukaryotic cells.

Although the model was presented almost 10 years ago, it is now that experimental evidences are supporting it.

Such model is important to rationalize artificial whole-genome computer design.

The team has published 17 articles (PLOS in computational Biology, Nucleic acid research, Journal of Molecular Biology), 9 book chapters and two patents.

### Assessment of the unit's academic reputation and appeal

The team is considered as one of the leading team in system biology.

The team has been involved in 9 international research grants and 6 national grants.

The team organized more than 15 meetings system biology. The team leader is invited in the most prestigious SynBio meetings (about 35 since 2008). The team leader coordinates the CNRS GDRE 513 on System Biology (2008-2015).

The team leader is also an expert working for the parliament and the ministry of research.

### Assessment of the unit's interaction with the social, economic and cultural environment

The team is involved in the Biointelligence project that involves such companies as Dassault Systems, Sanofi, Bayer.

The team leader is involved in social animation as “café des sciences”, article in general media, and is interviewed in radio such as France inter. He publishes several papers in journals such as Biofutur, Pour la Science, Buzz4bio, ...).

### Assessment of the unit's organisation and life

NA

### Assessment of the unit's involvement in training through research

Beside the involvement in the training organization of the whole unit, the team is strongly involved in the IGEM, the international context launched by MIT in 2003 for master student.

The team leader has founded the first Master in synthetic and systemic biology in France in 2007. He founded an European Master in Romania (ITEMS master at Politechnica of Bucharest)



## Assessment of the strategy and the five-year plan

The team wants to build on the knowledge that they have acquired and built on the solenoid model of genome in order to improve bioproduction of non-proteic molecules. Indeed, the bottleneck in metabolic reprogramming is to regulate in a concerted manner the different genes coding for the enzymes involved in the new and artificial pathways. It is necessary to insert the different genes in the genome at specific position. The team calls this new concept, the hyper-operons and is related to the 3D-colocalization of the genes involved in a given metabolic pathway.

The team is close to get excellent results on microbial genomes. The next step will be to extend such concepts to eucaryotic chromosomes.

## Conclusion

### ▪ Strengths and opportunities:

- Opening new paradigms in gene regulation;
- Impact of such paradigm in synthetic biology and more precisely in rational metabolic reprogramming;
- Role in the promotion of systemic and synthetic biology in France and in Europe.

### ▪ Weaknesses and threats:

- Size of the team as needed to compete at the international level in the field;
- Perpetuation of the theme of the team in the Institute;
- Relative small importance of this field in the national research strategy.

### ▪ Recommendations:

- Prepare the maintenance of the team in the institute;
- Nucleate a French institute in systemic and synthetic biology without walls if possible to reach for the french community a critical mass in synthetic and systemic biology.



**Team 4 :** METAMORPHOSYS

Name of team leader: Mr Nicolas POLLET

Workforce

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| <b>N1:</b> Permanent professors and similar positions                                   |                         | 1                       |
| <b>N2:</b> Permanent EPST or EPIC researchers and similar positions                     | 1                       | 1                       |
| <b>N3:</b> Other permanent staff (without research duties)                              |                         |                         |
| <b>N4:</b> Other professors (PREM, ECC, etc.)   |                         |                         |
| <b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) | 1                       |                         |
| <b>N6:</b> Other contractual staff (without research duties)                            |                         |                         |
| <b>TOTAL N1 to N6</b>   | <b>2</b>                | <b>2</b>                |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   | 2                       |                         |
| Theses defended   |                         |                         |
| Postdoctoral students having spent at least 12 months in the unit | 1                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken          |                         |                         |
| Qualified research supervisors (with an HDR) or similar positions | 1                       | 2                       |



## • Detailed assessments

### Assessment of scientific quality and outputs

The team leader joined the Genopole in 2008. The team is composed of 2 full time people and 2 PhDs. The team studies two aspects, the genes of the amphibian *Xenopus tropicalis* and the interactions between cellular identity and cell fate during metamorphosis. Several projects were developed during the period 2008-2013, such as the structure and dynamics of thyroid receptor during metamorphosis, the role of thyroid receptors during craniofacial development, the role of miRNA during *Xenopus* development, the use of *Xenopus* tadpole as an alternative model to study genetic diseases, the characterization of retrovirus in amphibians.

In addition the team has made important methodological contributions to the scientific community. The team leader has actively participated to the design and the development of the bioinformatics tools Xenbase and XenMARK. The first is a database which integrates different types of information concerning the genome, gene function, gene expression and the bibliography on *Xenopus*. The second is a new interactive database for gene expression patterns in *Xenopus*. These methodological works have a large impact on the international scientific community.

During the period 2008-2013 the team has published 27 articles in international journals. Two important articles are published with a consortium for the methodological advances (Science and Nature Biotech). The other articles are published in generalist journals (PNAS) or more specialized journals of developmental biology. In addition the team leader has published three chapters of books as last author.

### Assessment of the unit's academic reputation and appeal

The team leader was one of researchers who have built Xenbase and XenMARK. These databases have a large international impact. Two softwares were produced for these applications.

The team is involved in 2 European research projects and 3 national projects. At the European level the team leader is the coordinator of the 6th PCRDT X-OMICS : *Xenopus* functional genomics.

The team leader was the supervisor of the iGEM Evry team in 2012 and 2013. This team received in 2012 the gold medal for best model and best human practice.

Two post docs have joined the team and the team leader was co-organizer of the 14th international *Xenopus* conference (2012). The team leader is member of the *Xenopus* Genome project advisory board.

### Assessment of the unit's interaction with the social, economic and cultural environment

WATCHFROG a biotech company collaborating with the team share space with the team. This collaboration is supported by AFM. The team is also collaborating with AMAbiotics dedicated to bioremediations applications.

The team leader participates to more than 10 contracts and is involved in exhibitions and articles for the general public.

### Assessment of the unit's organization and life

NA

### Assessment of the unit's involvement in training through research

The team has hosted 2 PhD students, 2 post docs and two researchers for collaboration for one year.

The team leader was the supervisor of the iGEM Evry team in 2012.



## Assessment of the strategy and the five-year plan

The team proposes to promote the use of the *Xenopus* embryo and tadpole to study diseases and to test synthetic biology strategies for therapeutic applications. Two classes of diseases are chosen, neurological diseases (spinal muscular atrophy) and microbial infections.

These projects need a set of genetically encoded fluorescent sensors to be developed which can be targeted to specific neurons and to obtain gnotobiotic *Xenopus* embryos useful for microbiome engineering applications. These developments will be carried out in relation with the Watchfrog company.

## Conclusion

### ▪ Strengths and opportunities:

The team leader has a great implication in the life of the unit and for the community of developmental biologists using *Xenopus* as a model. He has actively participated to the design and development of 2 databases which are now indispensable for developmental biologists. The team has a great genetic engineering experience. This experience gives them the opportunity to develop numerous collaborations mainly in developmental biology as shown by the articles published.

### ▪ Weaknesses and threats:

During these last years the team leader has participated to several projects with *Xenopus* but some projects fall within the competence of the platform.

### ▪ Recommendations:

To clarify the exact goals of the team, the committee recommends to separate the research projects belonging directly to the team from the projects in collaboration depending on the activity of the platform.



**Team 5 :** XENOME

Name of team leader: Mr Piet HERDEWIJN

Workforce

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| <b>N1:</b> Permanent professors and similar positions                                   | 2                       | 2                       |
| <b>N2:</b> Permanent EPST or EPIC researchers and similar positions                     | 1                       | 1                       |
| <b>N3:</b> Other permanent staff (without research duties)                              |                         |                         |
| <b>N4:</b> Other professors (PREM, ECC, etc.)   |                         |                         |
| <b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) | 2                       | 2                       |
| <b>N6:</b> Other contractual staff (without research duties)                            | 3                       | 3                       |
| <b>TOTAL N1 to N6</b>   | <b>8</b>                | <b>8</b>                |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   |                         |                         |
| Theses defended   |                         |                         |
| Postdoctoral students having spent at least 12 months in the unit |                         |                         |
| Number of Research Supervisor Qualifications (HDR) taken          |                         |                         |
| Qualified research supervisors (with an HDR) or similar positions | 1                       | 1                       |



## • Detailed assessments

As the group has only been established within the past 4 years, only criterium C6 is evaluated.

### Assessment of the strategy and the five-year plan

The Xenome group is excellently positioned to maintain its world-leading role in Xenobiology. Its strategy and five-year plan is perfectly in line with this ambitious aim. The Xenome group will address the 5 key elements on the way towards a xenobiotic system:

- Definitive selection of “Xeno”nucleic acid (XNA) type;
- Elaboration of XMP uptake system;
- Engineering the metabolic dependency on a previtamin;
- Expression of an XNA gene in vivo using evolved polymerases;
- Synthesis of an XNA plasmid.

With the joint appointment of the Xenome group leader at iSSB and at the University of Leuven (Belgium), the Xenome group has all expertise, equipment and technology available to reach these ambitious aims. The excellence of this research proposal is underlined by the ERC advance grant awarded to the leader of the Xenome group.

### Conclusion

#### ▪ Strengths and opportunities:

- World-leading group in Xenobiology, unique expertise and skills available to keep up this position.
- Perfect synergies with Isthmus sarl at Evry;
- The Xenome group significantly contributes to the international visibility of Issb.

#### ▪ Weaknesses and threats:

- Sustainability of this world-leading Xenome biology at iSSB at risk given that the leader of the Xenome group is at iSSB during his ERC advanced grant and will retire within the next 5-7 years.
- No sufficient organic chemistry competency in place.

#### ▪ Recommendations:

Provided that iSSB aims to maintain Xenome biology research at the internationally leading level, it must provide an environment that makes it attractive to the leader of the Xenome group to stay affiliated to iSSB even after his retirement (a similar model as with Isthmus sarl might be possible). Furthermore, steps should be taken soon in order to find a successor for the leader of the Xenome biology group and to provide a package that allows attracting world-class experts in this field.





## 5 • Conduct of the visit

Visit date:

Start: February 5<sup>th</sup> 2014 at 8 AM

End: February 5<sup>th</sup> 2014 at 7 PM

Visit site:

Institution: Genopole Evry

Address : Biopark, Biocampus Evry

Specific premises visited:

NA

Conduct or programme of visit:

|            |  |
|------------|--|
| 8h30 -9h00 | Huis clos - Présentation de l'AERES au comité d'experts par le Délégué Scientifique AERES (DS) |
| 9h00 -9h15 | Devant l'unité, présentation du comité d'experts et présentation de l'AERES par le DS          |
| 9h15-9h50  | Présentation de l'unité, bilan et projet   |

### **AUDITION DES EQUIPES**

|                    |                            |
|--------------------|----------------------------|
| 9h50-10h25         | Bilan et projet équipe 1   |
| 10h25-11h00        | Bilan et projet équipe 2   |
| <b>11h00-11h15</b> | <b>Pause</b>               |
| 11h15-12h55        | Bilan et projet équipe 3   |
| 12h55-12h25        | Bilan et projet équipe 4   |
| 12h25-13h00        | Bilan et projet équipe 5   |
| <b>13h00-14h00</b> | <b>Déjeuner de travail</b> |

### **SESSION RENCONTRE AVEC LE PERSONNEL PERMANENT ET NON PERMANENT**

*Le comité se répartit en trois sous-groupes*

|                   |  |
|-------------------|--|
| <b>14h -14h45</b> | <b>Rencontre avec les ITA titulaires, CDD</b>  |
|                   | Auditoire : membres du comité d'experts, DS AERES, sans les tutelles, ni la direction        |
|                   | <b>Rencontre avec les doctorants et post-doctorants et/ou CDD « chercheurs », Ingénieurs</b> |
|                   | Auditoire : membres du comité d'experts, DS AERES, sans les tutelles, ni la direction        |



**Rencontre avec les chercheurs et enseignants chercheurs titulaires.**

Auditoire : membres du comité d'experts, DS AERES, sans les tutelles, ni la direction, ni les responsables d'Equipes

**14h45-15h00**      pause

**15h00-15h15**      Rencontre avec les représentants de l'École Doctorale:

Auditoire : membres du comité d'experts, DS AERES

**15h15-16h00**      Rencontre avec les représentants de la tutelle:

Auditoire : membres du comité d'experts, DS AERES

**16h00-16h30**      Rencontre avec la direction de l'unité

Auditoire : membres du comité d'experts, DS AERES

**16h30-18h30**      Réunion du comité à huis clos

Présence : membres du comité d'experts, DS AERES



## 6 • Supervising bodies' general comments



Evry, le 14 Mai 2014

Michel GUILLARD  
Administrateur Provisoire de l'Université  
d'Evry Val d'Essonne

4, Boulevard François Mitterrand  
91025 Evry Cedex

à :

Didier HOUSSIN  
Président  
Agence d'Évaluation de la Recherche  
et de l'Enseignement Supérieur  
20 rue Vivienne - 75002 PARIS

**Réf. AERES : S2PUR150007903**

**Direction de la Recherche, de la Valorisation et du  
Transfert**

Objet : Réponse au rapport du comité de visite de  
l'Institut de Biologie Systémique et Synthétique

Monsieur le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet de l'Institut de Biologie Systémique et Synthétique porté par M. Jean-Loup FAULON. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint.

Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, Monsieur le Président, à l'expression de mes salutations respectueuses.

M. Michel GUILLARD  
Administrateur Provisoire

**Prof. Jean-Loup FAULON**  
Directeur  
*Institut de Biologie Systémique et Synthétique*  
(CNRS FRE 3561)  
[Jean-Loup.Faulon@issb.genopole.fr](mailto:Jean-Loup.Faulon@issb.genopole.fr)  
01 69 47 44 47



## Institute of Systems & Synthetic Biology FRE3561

Comments on the report from the visiting AERES committee, February, 5 2014

Reference number of the report: E2015-EV-0911975C-S2PUR150007903-005042-RT

We first would like to thank the visiting committee for the detailed report, the careful evaluation, and the useful comments and recommendations.

The committee acknowledges that the young iSSB research unit has established itself during the past contract period into one of the largest synthetic biology laboratory in France with researchers of international reputation. The committee recognizes the unit is notoriously attractive to young scientists, actively involved in teaching and in technology transfer, and has worked out a coherent strategy and project for the next contract.

The first recommendation made by the committee is related to the contractualisation with private companies involved with iSSB. Agreements or contracts will be established between University of Évry-Val-d'Essonne (UEVE) and Isthmus, and between UEVE and Abolis since iSSB host some staff from these companies and in order to protect intellectual property from all involved players. Contracts/agreements or quotations/invoices are currently done for companies with whom iSSB carries out services. Concerning companies involved in European projects, the European Commission makes partners do sign consortium agreements.

The second recommendation concerns management organization. Following the advice of the committee, the management team will pay special attention to uncertainties regarding team leadership in the next contract. Yet, we note that team 2 leader has had experience in the past 5 years working at multiple locations without compromising research, and that team 5 leadership is secured for the next 5 to 7 years. The unit has planed in the next contract to attract several additional teams leaders and Team 1 leader will drop some of his commitments since his priority is on research. During the past 5 years, iSSB has grown by more than 300% and doubled the number of permanent staff, considering that the unit has been successful in the past to attract young talents and taking into account the progression of synthetic biology in Europe and France there is no reason to believe our growth will stop.

**Prof. Jean-Loup FAULON**  
Directeur  
*Institut de Biologie Systémique et Synthétique*  
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01 69 47 44 47



Also pointed out by the committee, during the previous contract, iSSB has raised about 9M€ through competitive funding giving an average of more than 900k€ per permanent staff (excluding administrative assistant), this accomplishment is due to our team structure. iSSB teams are working on different focus research topics and are highly motivated to push the boundaries of their own research fields, yet as acknowledged by the committee they are well integrated into an overall project and strategy. We believe this structure has worked for us in the past and has not prevented inter-team collaborations on projects, which have steadily grown since iSSB creation.

iSSB is however lacking technical staffs to maintain common resources and platforms. Following the third recommendation of the committee we will take advantage from the relocation of the unit to share analytical resources, skills and technical personnel with our future neighboring units.

Jean-Loup Faulon  
Directeur iSSB