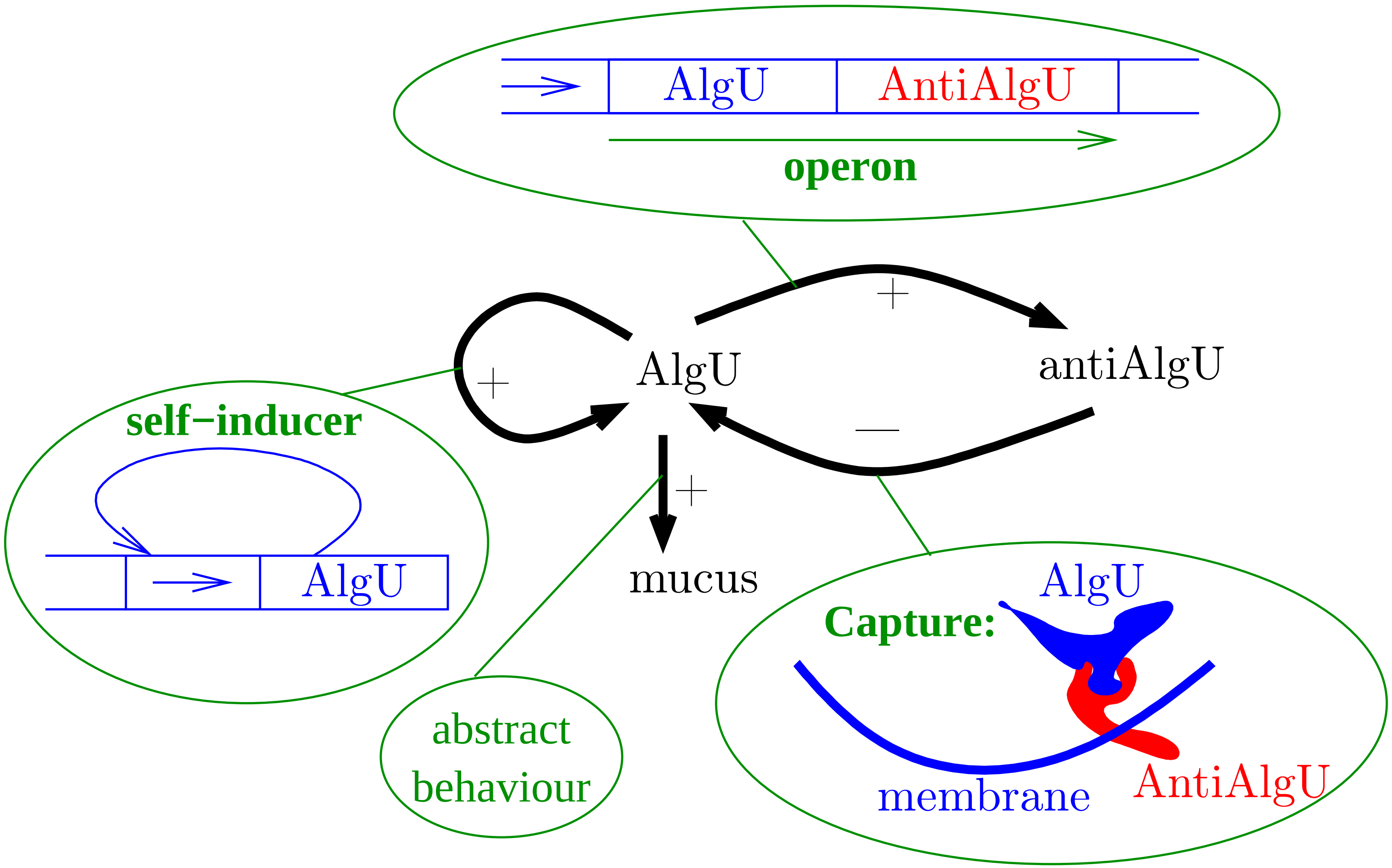
Formal Models of Biological Regulatory Networks. Example of Mucus Production in *Pseudomonas aeruginosa*

Gilles Bernot, Jean-Paul Comet, Janine Guespin
& the Observability Group

Programme d'ÉPIGÉNOMIQUE, Genopole®-Évry

Mucus Production in *P. aeruginosa*

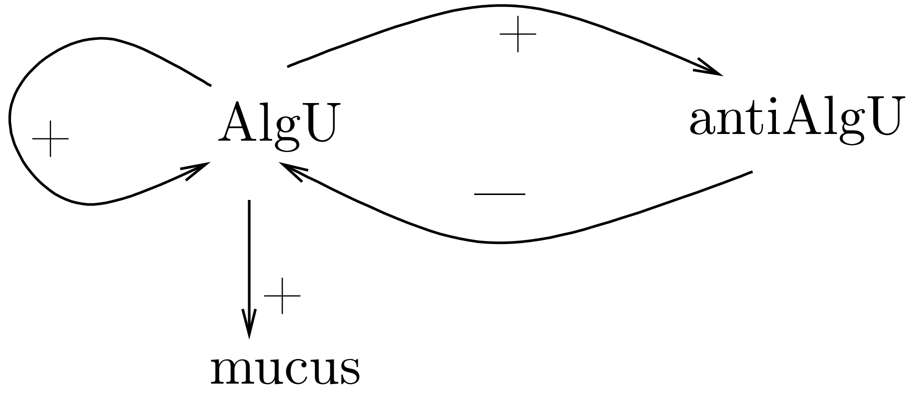


Static Graph & Dynamic Behaviour

Difficulty to predict the result of combined regulations

Difficulty to measure the strength of a given regulation

Example of "competitor" circuits



Positive *v.s.* Negative circuits

Even *v.s.* Odd number of "—" signs

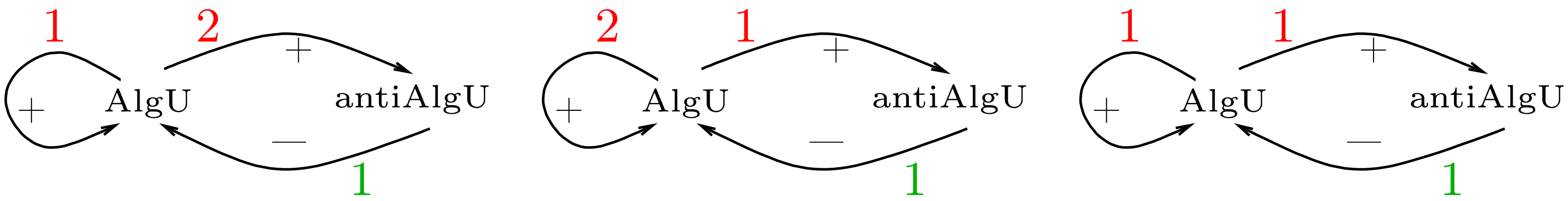
Multistationarity *v.s.* Homeostasy

Qualitative analysis: *René Thomas, Snoussi, . . . , Soulé, Richard*

Many additional parameters and thresholds pilot the behaviour

Parameters & Thresholds: often unknown

Thresholds for AlgU in *P.aeruginosa* are unknown:



and parameters are unknown:

$3^4 \times 2^2$ $\qquad$ $3^4 \times 2^2$ $\qquad$ $2^4 \times 2^2$

712 possible models

Some criteria exist to reduce the number of models,

but formal logic is needed to go further automatically

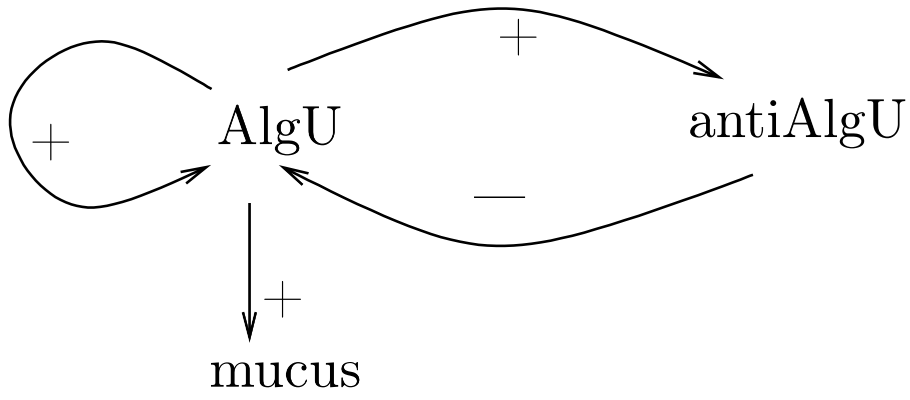
Theoretical Models $\leftrightarrow$ Experiments

Logic formulae are satisfied (or refuted) w.r.t. a set of paths from a given initial state

- They can be tested against the possible paths of the theoretical models ($M \models_\eta \varphi$)
- They can be tested against the biological experiments ($Biological\_Object \models_{experiment} \varphi$)

Logic formulae link theoretical models and biological objects together

The Epigenetic Hypothesis



One formula for each stable state:

$$(\text{AlgU} = 2) \Longrightarrow AXAF(\text{AlgU} = 2)$$
$$(\text{AlgU} = 0) \Longrightarrow AG(\neg(\text{AlgU} = 2))$$

Question 1, consistency: proved by *Model Checking*
→ 10 models among the 712 models are extracted by SMBioNet

Question 2: and *in vivo* ? …

Validation of the Epigenetic Hypothesis

Question 2 = to validate bistationnarity *in vivo*

Non mucoid state: $(\text{AlgU} = 0) \Longrightarrow AG(\neg(\text{AlgU} = 2))$

P. aeruginosa, with a basal level for AlgU *does not spontaneously produce mucus*: actually validated

Mucoid state: $(\text{AlgU} = 2) \Longrightarrow AXAF(\text{AlgU} = 2)$

Experiment:

to pulse AlgU *and then to test if mucus production remains.*

($\Longleftrightarrow$ to verify a hysteresis)

This proposal of experiment can be generated automatically

Concluding Slogans

- Behavioural *properties* are as much important as models for the modelling activity
- Modelling is significant only with respect to the considered experimental *reachability* and *observability*
- The bigger is the risk of *refutation*, the better are the "surviving" models (Popper), thus models should be "simple" with few non observable parameters (Occam)

Formal methods facilitate *abstraction* and consequently they simplify models

- They ensure *consistency* of the modelling activity
- They allow us to perform computer aided *validations* of models
- They take benefit of 30 years of researches in computer sciences