Continuous Valuations of Temporal Logic Specifications with applications to Parameter Optimization and Robustness Measures

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Lifeware Group

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Lifeware: hardware-software of the living

• How to compute with biochemical reactions?
  – Analog/digital computation
  – Compositionality and robustness of biochemical circuits
  – Programming artificial vesicles - Reprogramming living cells

• How to analyze natural cell processes as programs?
  – Cell signaling, cell cycle, circadian clock, gene expression, …
  – Temporal logic specification of the behaviour, parameter inference, robustness
  – Beyond describing, understanding natural circuits and their evolution

• How to control cell processes?
  – Microfluidic platform in an image analysis-model calibration-action loop
  – Optimal experimental design

• How to reason with cell populations?
  – Cell-to-cell variability analysis and control
  – Model of extrinsic/intrinsic noise
How to Compute with Biochemical Reactions?

- **Binding, complexation:** \( A + B \rightarrow C \)
  
  \( cdk1 + cycB \rightarrow cdk1cycB \)

- **Unbinding, decomplexation:** \( A \rightarrow B + C \)

- **Transformation, phosphorylation, transport:** \( A \rightarrow B \quad (A + E \rightarrow C \rightarrow B + E) \)
  
  \( cdk1cycB \rightarrow cdk1cycBp \)

- **Gene expression, synthesis:** \( A \rightarrow A + B \)
  
  \( E2Fa \rightarrow E2Fa + RNAcycA \)

- **Degradation:** \( A \rightarrow \_ \)
How to Compute with Biochemical Reactions?

- **Binding, complexation:**
  \[ A + B \xrightarrow{k_{AB}} C \]
  \( cdk1 + cycB \rightarrow cdk1cycB \)

- **Unbinding, decomplexation:**
  \[ A \xrightarrow{k_A} B + C \]

- **Transformation, phosphorylation, transport:**
  \( cdk1cycB \rightarrow cdk1cycBp \)
  \[ A \xrightarrow{k_A} B \quad \text{or} \quad A \xrightarrow{v.A/(k+A)} B \]

- **Gene expression, synthesis:**
  \[ E2Fa \rightarrow E2Fa + RNAcycA \]
  \[ A \xrightarrow{v.A^n/(k+A^n)} A + B \]

- **Degradation:**
  \[ A \xrightarrow{k_A} \_ \quad \text{or} \quad A \xrightarrow{v.A/(k+A)} \_]
Semantics of Reactions $A + B \xrightarrow{f(A,B)} C$

Continuous semantics: concentrations, continuous time evolution

Ordinary differential equations (ODE)

$$\frac{dA_i}{dt} = \sum_{r=1}^{n} f_r \times \delta_r(A_i)$$
Semantics of Reactions \[ A+B \xrightarrow{f(A,B)} C \]

Continuous semantics: concentrations, continuous time evolution

Ordinary differential equations (ODE)

\[ \frac{dA_i}{dt} = \sum_{r=1}^{n} f_r \times \delta_r(A_i) \]

Stochastic semantics: numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC)

\[ A, B \xrightarrow{p(S_i), t(S_i)} C++, A--, B-- \]
Semantics of Reactions  $A + B \xrightarrow{f(A,B)} C$

Continuous semantics: concentrations, continuous time evolution

Ordinary differential equations (ODE)

$$\frac{dA_i}{dt} = \sum_{r=1}^{n} f_r \times \delta_r(A_i)$$

Stochastic semantics: numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC)

$$A, B \xrightarrow{p(S_i), t(S_i)} C++, A--, B--$$

Petri net semantics: numbers of molecules

Multiset rewriting

CHAM [Berry Boudol 90] [Banatre Le Metayer 86]
Semantics of Reactions \( A + B \xrightarrow{f(A,B)} C \)

**Continuous semantics:** concentrations, continuous time evolution

Ordinary differential equations (ODE)

\[
\frac{dA_i}{dt} = \sum_{r=1}^{n} f_r \times \delta_r(A_i)
\]

**Stochastic semantics:** numbers of molecules, probability and time of transition

Continuous Time Markov Chain (CTMC)

**Petri net semantics:** numbers of molecules

Multiset rewriting

CHAM [Berry Boudol 90] [Banatre Le Metayer 86]

**Boolean semantics:** presence/absence

Asynchronous transition system
Abstraction Relationships

Theory of abstract Interpretation
Abstractions as Galois connections
[Cousot Cousot POPL'77]

Thm. Galois connections between the syntactical, stochastic, Petri Net and Boolean trace semantics
[FF Soliman CMSB'06, TCS'08]

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Abstraction Relationships

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Thm. Galois connections between the syntactical, stochastic, Petri Net and Boolean trace semantics

[FF Soliman CMSB'06, TCS'08]

If a behavior is not possible in the Boolean semantics
It is not possible in the stochastic semantics for any reaction rates
**Abstraction Relationships**

Thm. Under large number conditions the ODE semantics approximates the *mean* stochastic behavior [Gillespie 71]

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Abstraction Relationships

**Thm.** Under large number conditions the ODE semantics approximates the *mean* stochastic behavior [Gillespie 71]

- **Boolean traces**
- **Petri net traces**
- **Stochastic traces**
- **ODE traces**

**Hot topic:**
- Higher order moments
- ODE for mean, variance, ...

**Model cell-to-cell variability**
- Intrinsic and extrinsic noise
Hybrid Models and Hybrid Simulations

- Hybrid Boolean-continuous models (hybrid automata)
  Boolean gene expression + continuous protein activation

- Hybrid stochastic-continuous models (CTMC+ODE)
  Stochastic gene expression + continuous protein activation

Specification of hybrid simulators with *dynamic partitioning*
by reactions+events in SBML
[Chiang FF Huang Soliman 15 ACM TOMACS]
Quantitative Temporal Logic Specifications

• **Formalization of (imprecise) behaviors observed experimentally**
  - Quantitative temporal logic constraints $\text{FO-LTL}(\text{Rlin})$ [A. Rizk 2011 Thesis]
  - Stability $\mathbf{G}\varphi$; Reachability $\mathbf{F}\varphi$, thresholds $\mathbf{F}(\lbrack A \rbrack > 0.1)$,
  - Peaks of concentration $\exists V \mathbf{F}( \lbrack A \rbrack < V \land X( \lbrack A \rbrack = V \land X( \lbrack A \rbrack < V )))$
  - Amplitude, periods and phases as distance between peaks [Traynard Fages Soliman 14 CMSB]

• **Model verification**
  - Boolean symbolic model-checking [Chabrier Chiaverini Danos FF Schachter 04 TCS]
  - FO-LTL(Rlin) constraint solving [FF Rizk 08 TCS]
  - Continuous satisfaction degree of FO-LTL formulae [Rizk Batt FF Soliman 11 TCS]
  - Parameter sensitivity, robustness measures [Rizk Batt FF Soliman 09 Bioinformatics]

• **Model synthesis (parameter inference)**
  - Evolutionary search algorithm CMA-ES [Hansen 01] maximize satisfaction degree FO-LTL
  - FO-LTL satisfaction $\rightarrow$ dynamical model $\rightarrow$ quantitative predictions, control
  - FO-LTL unsatisfaction $\rightarrow$ model structure revision $\rightarrow$ contributions to biology
Model-Checking Generalized to Constraint Solving

\[ LTL(\mathbb{R}) \]

\[ \Phi = F([A] \geq 7) \land F([A] \leq 0) \]

Model-checking

the formula is false
Model-Checking Generalized to Constraint Solving

\[ LTL(\mathbb{R}) \quad \Phi = F(\text{[A]} \geq 7 \land F(\text{[A]} \leq 0)) \]

Model-checking

the formula is false

\[ QFLTL(\mathbb{R}) \quad \Phi^* = F(\text{[A]} \geq x \land F(\text{[A]} \leq y)) \]

Constraint solving

the formula is true for any \( x \leq 10 \land y \geq 2 \)
Model-Checking Generalized to Constraint Solving

\[ D_{\phi^*}(T) \]

**Validity domain** \( D_{\phi^*}(T) \) for the **free variables** in \( \phi^* \) [Fages Rizk CMSB’07]

**Violation degree** \( vd(T, \phi) = \text{distance}(val(\phi), D_{\phi^*}(T)) \)

**Satisfaction degree** \( sd(T, \phi) = \frac{1}{1 + vd(T, \phi)} \in [0, 1] \)

---

The diagram illustrates a model-checking and constraint solving scenarios. The validity domain \( D_{\phi^*}(T) \) is depicted with a green rectangle. The expressions for \( \Phi = F([A] \geq 7 \land F([A] \leq 0)) \) and \( \Phi^* = F([A] \geq x \land F([A] \leq y)) \) are shown, with Model-checking indicating the formula is false at points indicated by '×', and Constraint solving indicating the formula is true for any \( x \leq 10 \land y \geq 2 \).

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FO-LTL($R_{\text{lin}}$) Continuous Satisfaction Degree in [0,1]

Bifurcation diagram on $k_4$, $k_6$
[Tyson 91]

Continuous satisfaction degree in [0,1] of the LTL(R) formula for oscillation with amplitude constraint [Rizk Batt FF Soliman CMSB 08]

- **Parameter search** under LTL(R) constraints in high dimension (100 parameters) by continuous optimization (evolutionary algorithm CMA-ES)
- **Robustness** and **sensitivity** analyses w.r.t. LTL(R) specification
Robustness Measure Definition

Robustness defined with respect to:

- a biological system
- a functionality property $D_a$
- a set $P$ of perturbations

General notion of robustness proposed in [Kitano MSB 07]:

$$R_{a,P} = \int_{p \in P} D_a(p) \, \text{prob}(p) \, dp$$

Our computational measure of robustness w.r.t. LTL($\mathbb{R}$) spec:

Given an ODE model with initial conditions, a TL formula $\phi$ and a set of perturbations $P$ (on initial conditions or parameters),

$$R_{\phi,P} = \sum_{p \in P} sd(T(p), \phi) \, \text{prob}(p)$$

where $T(p)$ is the trace obtained by numerical integration of the ODE for perturbation $p$
Covariance Matrix Adaptation Evolutionary Strategy

- CMA-ES maximizes a black box fitness function \( sd(\phi) \) in continuous domain \( (k_i's) \) [Hansen Osermeier 01, Hansen 08]
- CMA-ES uses a probabilistic neighborhood and updates information in covariance matrix at each move

Generation 1  Generation 2  Generation 3

Generation 4  Generation 5  Generation 6
Packing of Complex Shapes with MiniZinc-CMAES

From simple shapes to continuous rotations and complex shapes defined by Bézier curves
Success Story in GPCR Signaling

- Reduced model with 4 observables, 4 mutations, known interactions
- Failure to find satisfying parameter values using quantitative temporal logic in BIOCHAM
- Revision of the model structure for 3 interactions, experimentally verified a posteriori

[D. Heitzler, …, FF, R. Lefkowitz, E. Reiter 2012 Molecular Systems Biology 8(590)]
Cell Cycle and Circadian Clock Coupling

- Influence of circadian clock on cell cycle: time gating for Mitosis through Wee1
- Influence of cell cycle on circadian clock?
  - Acceleration of the clock observed in fibroblasts in cells with fast cell cycle
  - Hypothesis of selective regulation of clock genes
  - Model-based prediction of up-regulation of RevErb around mitosis

### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>First set</th>
<th>Second set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis coefficient for Per</td>
<td>0.66</td>
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</tr>
<tr>
<td>Synthesis coefficient for Cry</td>
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<td>0.67</td>
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<tr>
<td>Synthesis coefficient for RevErb-α</td>
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<tr>
<td>Synthesis coefficient for Ror</td>
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<tr>
<td>Synthesis coefficient for Bmal1</td>
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<td>0.78</td>
</tr>
<tr>
<td>Duration</td>
<td>2.97h</td>
<td>2.81h</td>
</tr>
</tbody>
</table>
Model-based Control of Gene Expression in Yeast

Perception – learning – action loop on a microfluidic device:
1. Microscope, image analysis (cell tracking or population)
2. Model calibration (kinetic parameter optimization)
3. Osmotic pressure control (parameter optimization)

[Uhlendorf … Batt Hersen PNAS 109(35) 2012]
Beyond Describing Natural Circuits
Understanding them? Why those structures?

- Analog/Digital Computations
- MAPK signaling = Analog / Digital converter

- How to implement analog circuits with biochemical reactions?
- How to program with biochemical reactions?
Analog Arithmetic with Reactions?

- Infering reaction systems from ODEs [FF Gay Soliman 15 TCS]
- Compute $y = f(X)$
  1. $\frac{dy}{dt} = k*f(X) - k*y$ at steady state we will have $f(X) = y$
  2. Two reactions: $k*f(X)$ for $X \Rightarrow X + y$  $k*y$ for $y \Rightarrow _$
- Multiplication $z = x*y$
  1. $x*y$ for $x+y \Rightarrow x+y+z$
  2. $z$ for $z \Rightarrow _$
- Addition $z = x+y$
  1. $x$ for $x \Rightarrow x+z$
  2. $y$ for $y \Rightarrow y+z$
  3. $z$ for $z \Rightarrow _$
- Integral $z = \int x \, dt$
  1. $x$ for $x \Rightarrow x+z$

General Purpose Analog Computer (Shannon 41)
Logical Preconditions on Reactions?

- **Conjunction**
  
  \[ X \xrightarrow{A_\theta \land B_\theta} Y \]
  
  \[ X + A + B \rightarrow Y + A + B \]

- **Disjunction**
  
  \[ X \xrightarrow{A_\theta \lor B_\theta} Y \]
  
  \[ X + A \rightarrow Y + A \]
  \[ X + B \rightarrow Y + B \]

- **Negation**
  
  \[ \emptyset \xrightarrow{r_s} A' \]
  
  \[ A + A' \xrightarrow{r_f} A \]
  
  \[ (2A' \xrightarrow{r_f} A') \]
C Compiler into Reactions [Jiang et al 2012, 2013]

Division($A$, $B$)
begin
01 while $A \geq B$
02 $A := A - B$
03 $Q := Q + 1$
04 $R := A$
end

Main Reactions
01 while $[A] \geq [B]$
02 $(A + B \rightarrow D)$
03 $C \rightarrow Q + E$
04 $D \rightarrow F$
05 $E \rightarrow G$
06 $F \rightarrow B$
07 $G \rightarrow C$
08 $D \rightarrow R$

Preconditions
$\neg G_\theta$
$A_\theta \land \neg B_\theta$
$\neg C_\theta$
$\neg D_\theta$
$\neg E_\theta$
$\neg F_\theta$
$\neg A_\theta$


C Compiler into Reactions [Jiang et al 2012, 2013]

\[ \text{GreatestCommonDivisor}(A, B) \]
\[
\begin{align*}
\text{begin} & \quad \text{while } A \neq B \\
& \quad \text{if } A > B \\
& \quad \quad A := A - B \\
& \quad \text{else if } B > A \\
& \quad \quad \text{swap}(A, B) \\
& \quad \quad \text{GCD} := A \\
\text{end}
\end{align*}
\]

Main Reactions

01 \quad \text{while } [A] \neq [B]
02 \quad (A + B \rightarrow C)
03 \quad \text{if } [A] > [B]
04 \quad C \rightarrow D
05 \quad D \rightarrow B
06 \quad \text{else if } [B] > [A]
07 \quad C \rightarrow E
08 \quad B \rightarrow G
09 \quad E \rightarrow F
10 \quad G \rightarrow A
11 \quad F \rightarrow A + B
12 \quad C \rightarrow \text{GCD}

Preconditions

\[ \neg D_{\theta} \land \neg F_{\theta} \]
\[ A_{\theta} \land \neg B_{\theta} \]
\[ \neg C_{\theta} \]
\[ \neg A_{\theta} \land B_{\theta} \]
\[ \neg C_{\theta} \land \neg A_{\theta} \]
\[ \neg B_{\theta} \]
\[ \neg E_{\theta} \]
\[ \neg G_{\theta} \]
\[ \neg A_{\theta} \land B_{\theta} \]

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General Purpose Analog Computer [Shannon 41]

Idealization of an analog computer: Differential Analyzer circuit built from:

- *A constant unit*: \[ k \times k \]
- *An adder unit*: \[ u + v \]
- *An multiplier unit*: \[ uv \]
- *An integrator unit*: \[ \int uv \, dv \]

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Church-Turing Thesis for Analog Computation

**Definition**

$f$ is **computable** by a GPAC iff $\exists p, q$ polynomials s.t. $\forall x \in \mathbb{R}$, the solution $y = (y_1, \ldots, y_d)$ of:

\[
\begin{aligned}
    y' &= p(y) \\
    y(t_0) &= q(x)
\end{aligned}
\]

satisfies $f(x) = \lim_{t \to \infty} y_1(t)$.

**Example**

![Graph showing the relationship between $q(x)$, $y(t)$, and $f(x)$ over time]

**Theorem (Bournez, Campagnolo, Graça, Hainry)**

$f$ is GPAC-computable functions iff it is computable (in the sense of Computable Analysis).
Purely Analog Characterization of Ptime!

[Pouly Bournez Graca 2015]

**Definition**

$f$ is **poly-computable** by a GPAC iff $\exists p, q$ polynomials s.t. $\forall x \in \mathbb{R}$, the solution $y = (y_1, \ldots, y_d)$ of:

$$
\begin{cases}
    y'(t) = p(y(t)) \\
    y(t_0) = q(x)
\end{cases}
$$

satisfies that:

- $\|f(x) - y_1(t)\| \leq e^{-\mu t}$ when $t \geq \text{poly}(\|x\|, \mu)$
- $\|y(t)\| \leq \text{poly}(\|x\|, t)$

**Theorem**

$f$ is poly-computable if and only if it is computable in polytime in the sense of Computable Analysis.
Cosine Function Graph Generation

Example in BIOCHAM

```plaintext
compile_wgpac(cos10 ::
    integral integral -1*cos10, 10).
present(cos10).

[0] 10*[x_auto_2]*[cos]for _=[x_auto_2+cos]=>x_auto_1
[1] 10*[x_auto_1]for x_auto_1=>_
[2] _=[x_auto_1]=>x_auto_0
[3] _=[x_auto_0]=>cos
```
Cosine Function Graph Generation

Blocks representation

Example in BIOCHAM

```plaintext
compile_wgpac(cos100 ::
    integral integral -1*cos100, 100).
present(cos100).
```
Linear Time Invariant Systems

Definition: Laplace transform

$$\forall s \in \mathbb{R}_+, \quad \mathcal{L}f(s) = \int_0^{+\infty} e^{-st} f(t) dt$$

→ Laplace transform of linear and time invariant systems are rational fractions of $\mathbf{R}(s)$.

Definition: Transfer function

The transfer function of a LTI system with input $U$ and output $Y$ is the rational fraction $H$ such that $Y(s) = H(s)U(s)$. It is said to be strictly proper when its degree is negative.
Transfer Function of Reaction Impl.  [Jiang et al 2015]

<table>
<thead>
<tr>
<th>Block Diagram</th>
<th>Normal Transfer Function</th>
<th>CRN Transfer Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\frac{k_1}{k_0}$</td>
<td>$\frac{k_1}{s + k_0}$</td>
</tr>
<tr>
<td>$\frac{k_1}{k_0}$</td>
<td>$\frac{k_1 k_3}{k_0 s + k_2 k_3}$</td>
<td>$\frac{k_1 k_3}{s^2 + k_0 s + k_2 k_3}$</td>
</tr>
<tr>
<td>$\frac{k_1}{k_0}$</td>
<td>$\frac{k_1 s}{k_0 s + k_2 k_3}$</td>
<td>$\frac{k_1 s}{s^2 + k_0 s + k_2 k_3}$</td>
</tr>
</tbody>
</table>
Compiling Transfer Functions into Reactions

Compiler principle:
1. 'break' the transfer function into simple functions, this step is performed by computing the partial fraction expansion of $H$;
2. each of these simple functions consist of a chemical network with input $u$ and output $y_i$;
3. recombine the individual outputs $y_i$ to get $y$. 
Compiling Transfer Functions into Reactions

- Write $H = \sum H_i$ where $H_i$ are simple functions, that is either of the form $\frac{a}{(s+\alpha)^n}$ or $\frac{a}{(s^2+\beta s+\gamma)^m}$ or $\frac{bs}{(s^2+\beta s+\gamma)^m}$.

- Each of these functions can in turn be written a product of elementary functions, that is either of the form $\frac{a}{s+\alpha}$ or $\frac{a}{s^2+\beta s+\gamma}$ or $\frac{bs}{s^2+\beta s+\gamma}$, denoted respectively by $(1,0)$, $(2,0)$ and $(2,1)$.

- Product corresponds to series composition of modules ;

- Sum is performed by parallel computation.
Remark: The summing node is chemically implemented through the reactions $y_i \xrightarrow{k} y_i + y$ for each local output $y_i$ and $y \xrightarrow{k} \emptyset$. Therefore one has

$$Y(s) = \frac{k}{s + k} \sum Y_i(s)$$

This unwanted factor can be compensated by computing $\hat{H} = \frac{s + k}{k} H$ instead of $H$. 

Example: a first-order filter \( \frac{1}{s+2} \), 'naive' implementation

Biocham

\[
\text{compile_wgpac([y1 :: integral x1,}
\]
\[
x1 :: u1 + (-2)\ast y1],
\]
\[
10).
\]

\text{present(u1).}

Illustration of time response: \( y_1(t) \)
Example: a first-order filter \( \frac{1}{s+2} \)

Biocham

```
compile_transfer_function(1/(s+2), u1, y1).
present(u1).
```

Illustration of time response: \( y_1(t) \)
Comparison of the created systems

naive

[0] _=[x1]=>y1
[1] 10*[{x_auto_4}]*[{y1} for _={x_auto_4+y1}]=>x_auto_3
[2] 10*[{x_auto_3} for x_auto_3]=>_ 
[3] 10*[{u1} for _={u1}]=x1
[4] 10*[{x_auto_3} for _={x_auto_3}]=x1
[5] 10*[{x1} for x1]=>_ 

transfer function specific

[0] _=[u1]=>y1
[1] 2*[{y1} for y1]=>_ _
Example: a second-order filter $\frac{1}{1+s+s^2}$, 'naive' implementation

```python
Biocham

compile_wgpac([y1 :: integral x1, x1 :: u1 + (-1)*y1, y2 :: integral y1, u1 :: u2 + (-1)*y2], 10).
present(u2).

Illustration of time response: $y_2(t)$
```

![Graph](image-url)
Example: a second-order filter \[ \frac{1}{1+s+s^2} \]

Biocham

```plaintext
compile_transfer_function(1/(s*s+s+1), u2, y2).
present(u2).
```

Illustration of time response: \( y_2(t) \)

```
_=u2]=>x1,
-1*[y2]for _=[y2]=>x1,
_=x1]=>y2
x1=>_
```
Enzymatic Computation in Non-Living Vesicles

- **Biosensor design and implementation in non-living vesicles**
  [Franck Molina lab CNRS Sys2Diag Montpellier]

- Implementation of linear I/O systems, PI controllers and simple programs?
  → Issue of approximation and compositionality
  → Issue of reaction code optimization (number of species and reactions)

- Comparison of synthetic programs with natural programs
  → Multiple functions of a circuit?
  → Evolution history? Evolution capacity?
Thank you!

Et désolé si j’étais à l’ouest