Logic-based Multi-Objective Design of Chemical Reaction Networks

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Overview

System Design

System Design is a methodology useful to prototype an architecture which satisfies a given requirement.

Fields of application:

- Industries : CAE software
- Synthetic Biology and Systems Biology
- Complex systems (in general)

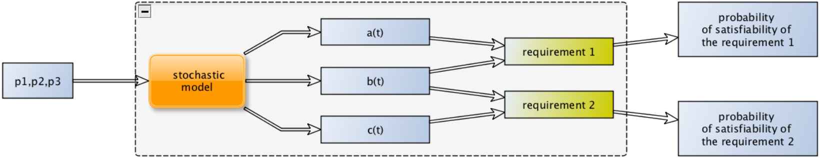
Motivations:

- Cost reduction and prototyping time reduction.

System Design

1. Define a model of the real systems we want to build up.
2. Define the requirements we want to address.
3. Tuning the parameters of the model in order to satisfy the given requirements.

1. Chemical Reaction Networks (CRN).
2. Signal Temporal Logic interpreted over the path generated by the CRN.
3. The parameters are related to the chemical reaction rates.



The goal

Maximize the probability of satisfaction of different requirements.

Usually the systems design procedure will involve conflicting requirements.

Multi-objective Approach

Conflicting requirements are optimized simultaneously.

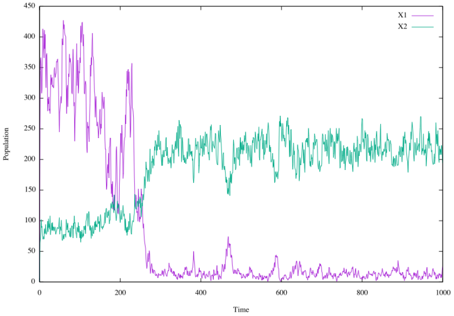
The stochastic model: Chemical Reaction Network (CRN)

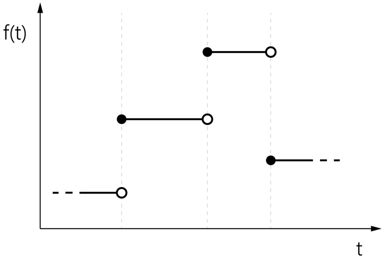
Consider a CRN as a tuple $(\mathcal{S}, \mathbf{X}, \mathcal{R}, \theta\ )$

$$r_j : u_{j,1}s_1 + \ldots + u_{j,n}s_n \xrightarrow{\alpha_j(\mathbf{x},\theta)} w_{j,1}s_1 + \ldots + w_{j,n}s_n,$$

- $\theta = (\theta_1, \ldots, \theta_k)$ is the vector of (kinetic) parameters, taking values in a compact hyperrectangle $\Theta \subset \mathbb{R}^k$.

Simulation Example





The requirements: Signal Temporal Logic (STL)

Signal temporal logic is:

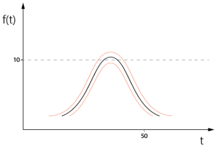
- a discrete linear time temporal logic.
- the atomic predicates are of the form $\mu(\vec{X}):=[g(\vec{X}) \geq 0]$ where $g : \mathbb{R}^n \rightarrow \mathbb{R}$ is a continuous function.
- the syntax is

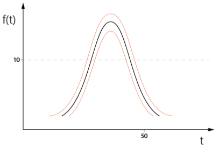
$$\phi := \perp \mid \top \mid \mu \mid \neg\phi \mid \phi \vee \phi \mid \phi \mathbf{U}_{[T_1,T_2]}\phi, \tag{1}$$

Example

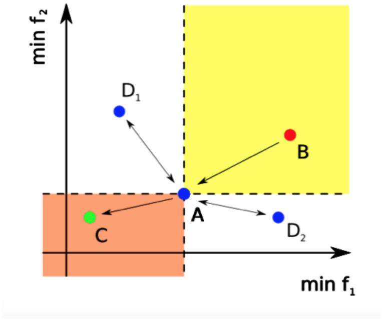
$$\phi_1 := F_{[0,50]}|X_1 - X_2| > 10$$

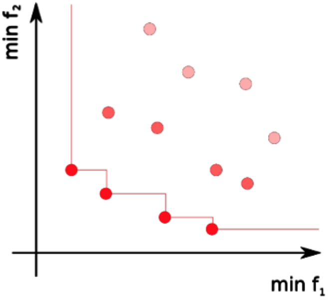
1. **The Booleans semantics:** if a given path satisfies or not a given STL formula.
2. **The Quantitative semantics:** How much a given path satisfies or not a given STL formula.





Multi-objective problems





- C dominates A
- A dominates B
- There is no dominance relation among A, D_1, D_2.

Pareto Frontier

The pareto frontier is the set of non dominated points.

Three Strategies

Probability

$$P(\Phi|\theta) = (P(\phi_1|\theta), P(\phi_2|\theta), \ldots, P(\phi_k|\theta))$$

$$P(\phi_i|\theta) = \frac{\sum_{j=1}^{N} \chi(\phi_i, \vec{x}_j, 0)}{N}$$

Average Robustness Degree

$$\hat{\rho}(\Phi|\theta) = (\hat{\rho}(\phi_1|\theta), \hat{\rho}(\phi_2|\theta), \ldots, \hat{\rho}(\phi_k|\theta))$$

$$\hat{\rho}(\phi_i|\theta) = \frac{\sum_{j=1}^{N} \rho(\phi_i, \vec{x}_j, 0)}{N}$$

The multiobjective problem

$$\max P(\Phi|\theta) = (\max P(\phi_1|\theta), \max P(\phi_2|\theta), \ldots, \max P(\phi_k|\theta))$$

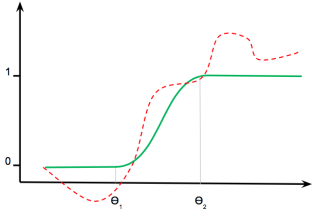
Strategies

- Direct Probability Approach (DpA)
- Direct Robustness Approach (DrA)
- Mixed Approach (MA)

Behind the Three strategies II

The idea consists of using the robustness score:

- To escape from probability-zero flat zone
- To prefer more robust outcome in probability-one flat zone.

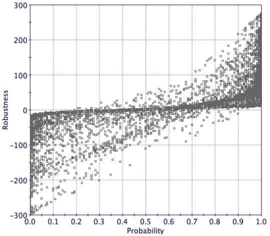


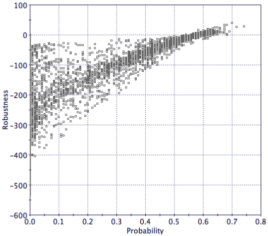
Question

Direct Robustness Approach is the solution?

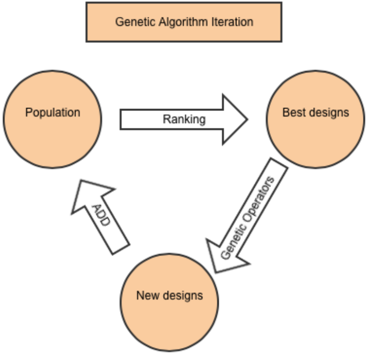
Answer

Almost, in fact it will produce under optimal results...





Mixed Approach



Steps

- Ranking using the **Pareto dominance**
- Best designs are selected
- New generation of designs is created using the genetic operators (**mutation** and **crossover**)
- The new generation is append to the entire population

Mixed approach idea

Modify the usual Pareto Dominance as follows:

- **if** $\{P(\Phi|\theta_1) == P(\Phi|\theta_2)\}$ then **return** $\{\ \hat{\rho}(\Phi|\theta_1)$ dominates $\hat{\rho}(\Phi|\theta_2)?\ \}$
- **else return** $\{\ P(\Phi|\theta_1)$ dominates $P(\Phi|\theta_2)?\ \}$

Genetic Toggle Switch: Results

- Two populations X_1 and X_2.
- The reaction depends on 4 parameters.
- Two stable equilibria $X_1 > X_2$ or $X_1 < X_2$

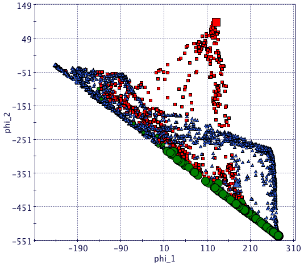
Higher is the difference among X_1 and X_2 more stable is the systems.

$$\begin{aligned}
r_1 &: \quad \emptyset \xrightarrow{\alpha_1} X_1 & \alpha_1 &= 1 \\
r_2 &: \quad \emptyset \xrightarrow{\alpha_2} X_2 & \alpha_2 &= 1 \\
r_3 &: \quad X_1 \xrightarrow{\alpha_3} \emptyset & \alpha_3 &= \frac{a_1 N^{b_1+1}}{N^{b_1} + X_2^{b_1}} \\
r_4 &: \quad X_2 \xrightarrow{\alpha_4} \emptyset & \alpha_4 &= \frac{a_2 N^{b_2+1}}{N^{b_2} + X_1^{b_2}}
\end{aligned}$$

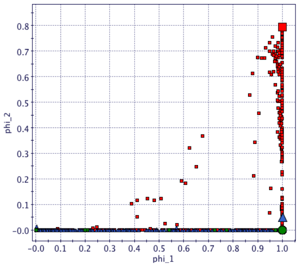
STL requirements

$$\begin{aligned}
\phi_1 &:= F_{[0,1000]} \quad |X_1 - X_2| > 300 \\
\phi_2 &:= F_{[0,300]} \quad G_{[0,50]}(X_1 > X_2) \wedge F_{[300,550]} G_{[0,50]}(X_1 < X_2).
\end{aligned}$$

Genetic Toggle Switch: Results



(c) Robustness Space



(d) Probability Space

Analysis

- **DpA:** it cannot escape from probability-zero flat zone.
- **DrA:** the optimization explores a useless area.
- **MA:** reach an optimum point.

Criticism to the Robustness Semantics

Case 1

$$\forall \theta \in D, \forall t \in [0,30] f(t) \in [0,1]$$
$$\phi_1 := F_{[0,30]} f(t) > 0.5$$

Case 2

$$\forall \theta \in D, \forall t \in [0,30] g(t) \in [-3,-2]$$
$$\phi_2 := F_{[0,30]} g(t) > 1$$

Implication 1

$$\rho(\phi_1|\theta) \in [-0.5, 0.5]$$

Implication 2

$$\rho(\phi_2|\theta) \in [-4, -3]$$

Robustness of the conjunction

$$\rho(\phi_1 \wedge \phi_2|\theta) = min(\rho(\phi_1|\theta), \rho(\phi_2|\theta)) = \rho(\phi_2|\theta)$$

The quantitative semantic of the conjunction does not take in account the requirement ϕ_2.
Maximizing it means maximize only the robustness of ϕ_2.

Criticism to the Robustness Semantics

The problem

The robustness score is sensitive to the different length-scale of the atomic predicates

- normalizing them accordingly to the length-scale is not possible.

Idea

Use the multi-objective approach!

- Decompose Φ:

$$\textbf{from } \Phi \textbf{ to } \phi_1 \wedge \phi_2 \wedge \cdots \wedge \phi_n$$

- Define an optimization but ...

  ...instead of $\max \rho(\phi_1 \wedge \phi_2 \wedge \cdots \wedge \phi_n | \theta)$ **do** $(\max \rho(\phi_1|\theta), \max \rho(\phi_2|\theta), \ldots, \max \rho(\phi_n|\theta))$

Summary and Conclusion

Summary:

- System design as multi-objective optimization.
- Three approaches: DpA, DrA, MA.
- Genetic Toggle Switch Example.
- The "weakness" of the robustness score: the length scale problem.

Conclusion:

- The robustness score could be useful to escape from flat zone of the probability space.
- Using both the probability and the robustness score is a promising choice.

Future Works:

- Study the feasibility of the multi-objective approach to deal with the length-scale problem of the robustness semantics.
- Investigate the use of more refined optimization methods to deal with noise.

Thank You