

Syntax-guided optimal synthesis for chemical reaction networks

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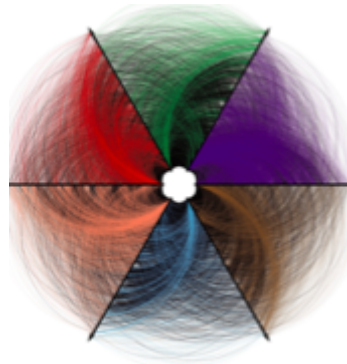
motivation: uncertainty in biological models

“SYSTEMS” UNCERTAINTY: partial knowledge of the system (e.g. unknown parameters, interactions)

AIM: fill knowledge gaps to derive predictive models consistent with observations

EXAMPLES: network reconstruction, parameter estimation

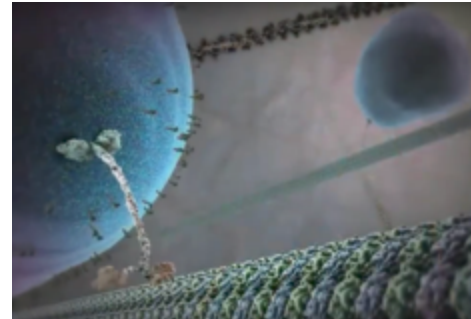
Human Transcription
Factor Regulatory Network
[Neph et al, Cell 150(6),
2012]



“SYNTHETIC” UNCERTAINTY: how to engineer living organisms to achieve specific functions?

AIM: automated design of correct-by-construction, optimal, biological processes/devices

EXAMPLES: synthetic biology, DNA programming, molecular computing



Molecular walker
from "Inner Life
of the Cell,"
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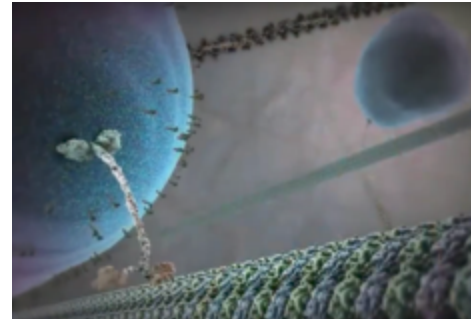
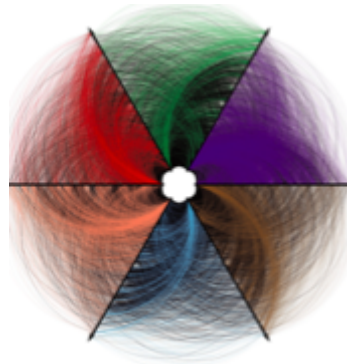
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“SYSTEMS” UNCERTAINTY: partial knowledge of the system (e.g. unknown parameters, interactions)

“SYNTHETIC” UNCERTAINTY: how to engineer living organisms to achieve specific functions?

NEED FOR A MODELLING LANGUAGE ABLE TO CAPTURE UNCERTAINTIES AND AUTOMATED ANALYSIS METHODS TO RESOLVE THEM

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chemical reaction networks (CRNs)



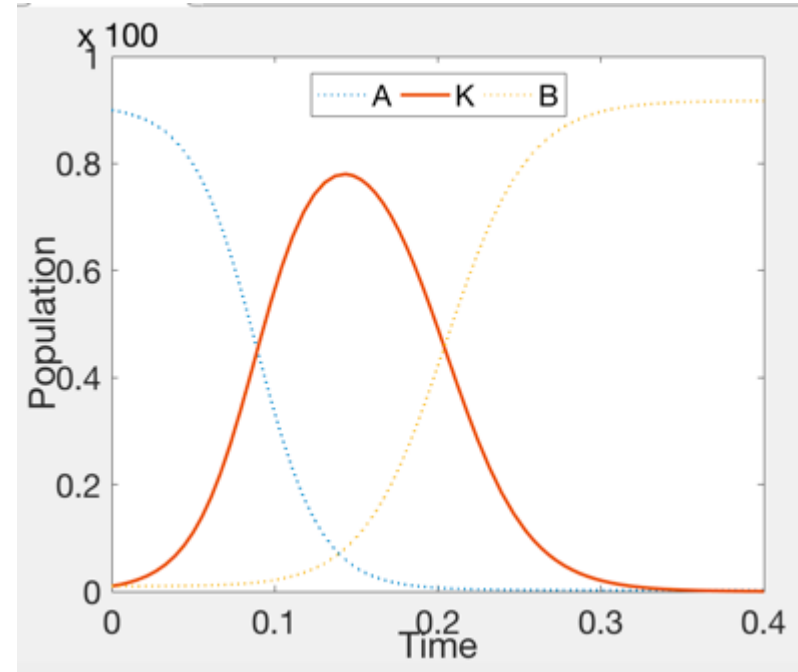
- CRNs are a **fundamental model for natural systems** (chemical, genetic, metabolic, ...)
- **Fundamental computational structure** (equivalent to Petri Nets, Vector Addition Systems, ...)
- Can be “**compiled**” into DNA
- Biochemical interactions are **inherently stochastic** (CRN semantics typically described as continuous-time Markov chains)

problem: synthesis of CRNs

How to synthesize a network where

- Species K exhibits a **bell-shaped profile** (or an inflection point, local optimum, ...)
- Variance of species B $>$ variance of A
- Species B is monotonic
- ...
- ... and the network uses the least number of species/reactions (**notion of cost/optimality**)

What if both rate coefficients and network structure are unknown?



challenges of CRN synthesis

- We need quantitative reasoning while keeping stochasticity
- Classical CTMC semantics of CRNs is not scalable
- **State-of-the-art approaches cannot deal with synthesis of both rate and structure**

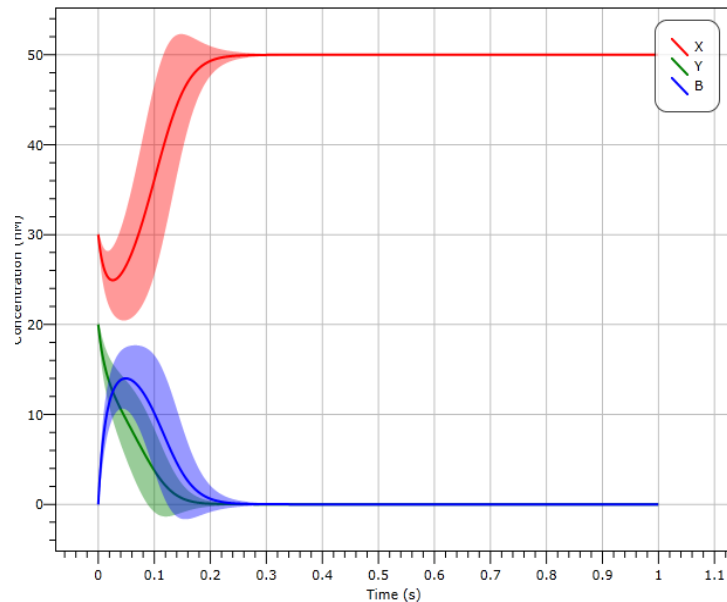
Related work

[Ceska et al., CMSB'14] CRN parameter synthesis as “parametric extension” of probabilistic model checking (can't synthesize structure)

[Dalchau et al., DNA, 2015] Structure and rates synthesized in two separate stages: inefficient, incomplete

idea 1: Linear Noise Approximation

- Stochastic semantics traditionally given by Chemical Master Equation or CTMC
- **Linear Noise Approximation (LNA)** produces ODEs for mean and covariances of species concentration over time
- **Superior scalability**, while keeping stochasticity



idea 2: syntax-guided program synthesis (SyGuS)

- **SyGuS**: correctness specification + syntactic template for the program [Alur et al. “Syntax-guided synthesis”]
- **Program sketching** [Solar-Lezama et al., PLDI’05]: programming with holes and variables (to model incomplete information), resolved using constraint solving (SMT)

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CRN sketch example



our approach

Solve CRN sketches with **SMT over non-linear reals and ODEs (SMT-ODE)**,
iSAT(ODE) solver [Eggers et al., ATVA'08]

Contributions:

- First sketching language for synthesis of CRNs
- Specification language
- Novel optimal synthesis problem, encoded as an SMT-ODE solving problem through LNA
- Prototype + evaluation on 3 case studies

sketching language – Bell shape example

- Finite set of **species** (mandatory and optional)
- **Declared variables** for species (λ_i), stoichiometric coefficients (c_i), and rates (k_i)
- Variables express the uncertainty
- **Constraints** on initial state and variables

$$\Lambda_m = \{K\} \text{ and } \Lambda_o = \{A, B\}$$

$$\begin{aligned} \lambda_1, \lambda_2 &: \{A, B\}, \\ c_1, \dots, c_4 &: [0, 2], \\ k_1, \dots, k_3 &: [0, 0.1] \end{aligned}$$

$$\begin{aligned} K_0 = 1 \wedge A_0, B_0 &\in [0, 100] \\ \lambda_1 \neq \lambda_2 \wedge c_1 < c_2 \wedge c_3 > c_4 \end{aligned}$$

sketching language – Bell shape example

Species

$$\Lambda_m = \{K\} \text{ and } \Lambda_o = \{A, B\}$$

Declared variables

$$\lambda_1, \lambda_2: \{A, B\},$$

$$c_1, \dots, c_4: [0, 2],$$

$$k_1, \dots, k_3: [0, 0.1]$$

Constraints

$$K_0 = 1 \wedge A_0, B_0 \in [0, 100]$$

$$\lambda_1 \neq \lambda_2 \wedge c_1 < c_2 \wedge c_3 > c_4$$

Reaction sketch



Example instantiation



Inline, implicit
declarations
($\{0, 1\}, ?, [1, 2]$)

Choice between
 λ_2 and $[1, 2]K$

specification language

- A property describes the required temporal profile as a sequence of phases
- Supports constraints about the expected number and variance of molecules, and their derivatives

Bell shape (2 phases):

1

$$\text{inv}_1 \equiv E^{(1)}[K] \geq 0$$

$$\text{pre-post}_1 \equiv E^{(1)}[K]' = 0$$

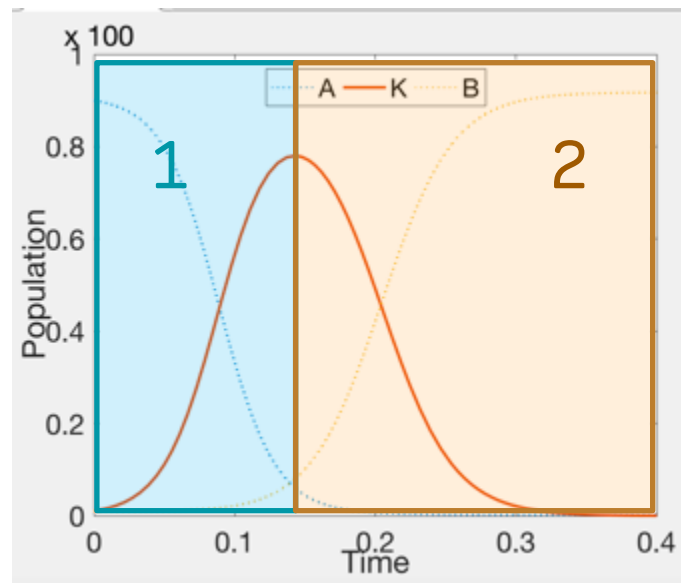
$$\wedge E[K]' > 0$$

2

$$\text{inv}_2 \equiv E^{(1)}[K] \leq 0$$

$$\text{pre-post}_2 \equiv E[K]' \leq 1$$

$$\wedge T' = 1$$



optimal synthesis

PROBLEM: OPTIMAL SYNTHESIS OF CRNs

IN: Sketch S + Correctness specification ϕ + Cost function G

OUT: Instantiation I of S that satisfies ϕ (if exists) and is minimal w.r.t. G

Structural complexity cost:

$$\text{COST} = k_1 * (\text{num. of optional species in } I) + k_2 * (\text{total num. of reactants in } I) + k_3 * (\text{total num. of products in } I)$$

Based on cost of implementation in DNA [Cardelli et al., MSCS '13]

synthesis algorithm

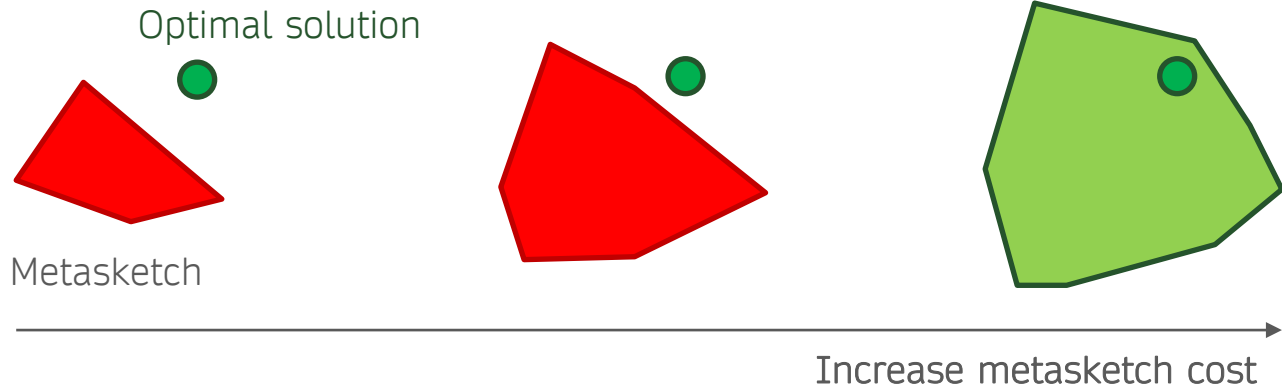
- Builds on the notion of **meta-sketch = sketch + cost constraints**
- **Cost constraints reduce search space** size for SMT solver and improve runtime

ALGORITHM

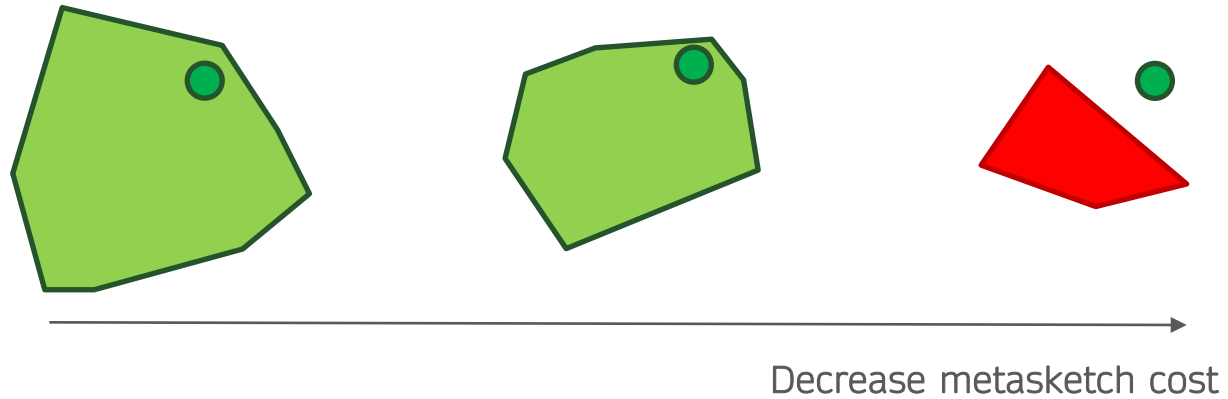
- Repeated calls to the solver under different cost constraints
- Generalized solving scheme:
 - **Bottom-up**: increase metasketch cost until SAT
 - **Top-down**: decrease metasketch cost until UNSAT
 - **Binary search**: use both SAT and UNSAT witnesses to bound optimal cost
- “Smart” UNSAT witness generation

synthesis algorithm

Bottom-up:

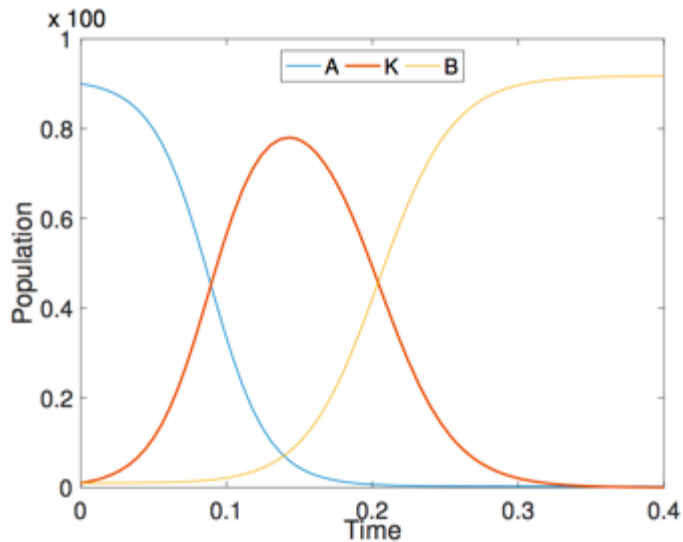
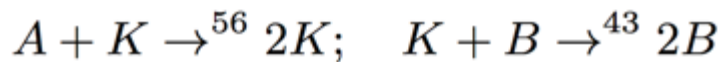


Top-down:

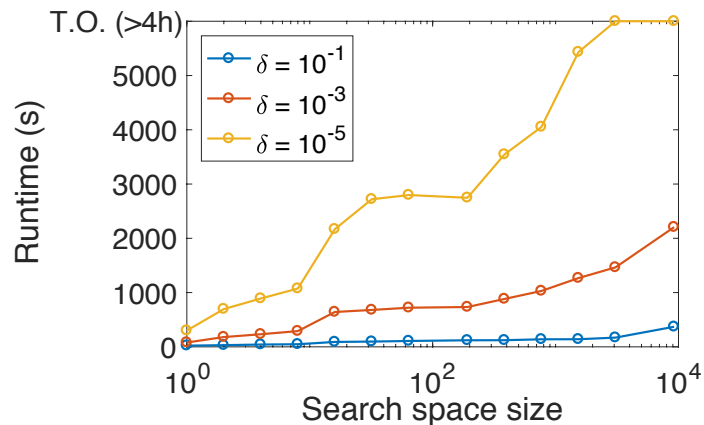


bell shape

Synthesized Network:



Performance:

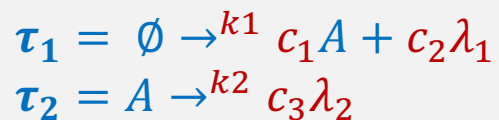


- Bottom-up more effective, since UNSAT instances (due to the cost) are faster to solve
- Cost constraints reduce avg solving time for each call of between 37 and 83%

super Poisson

- AIM: synthesize “CRN implementation” of a stochastic process
- Super-Poisson process (variance > expectation)

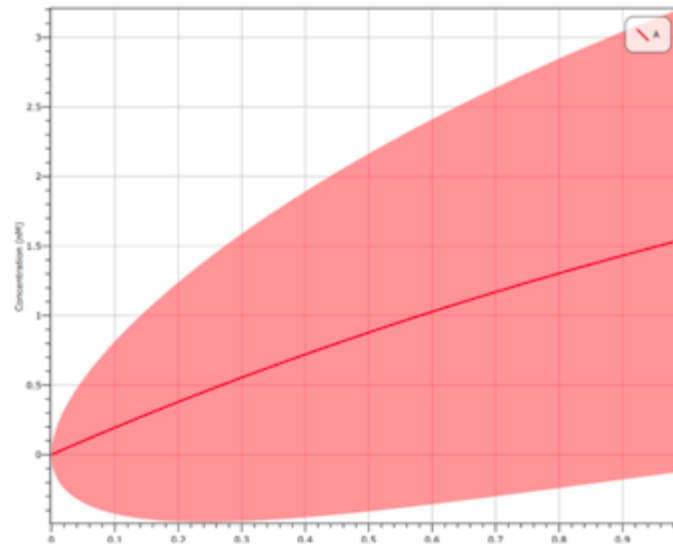
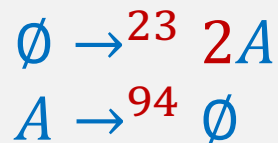
Sketch:



Specification:

$$\begin{aligned}inv_1 &\equiv C[A] > E[A] \\ pre - post_1 &\equiv T' = 1\end{aligned}$$

Solution:

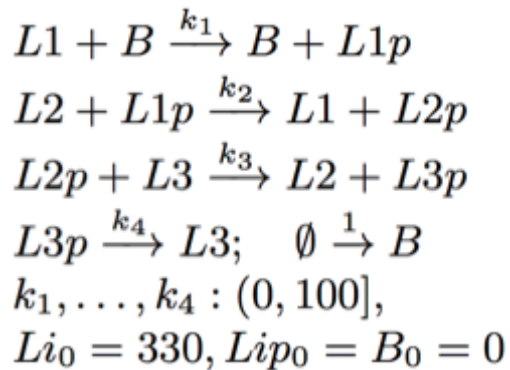


SOLVED IN 4 seconds!!!
Encoding size: 10 ODEs +
search space size 288

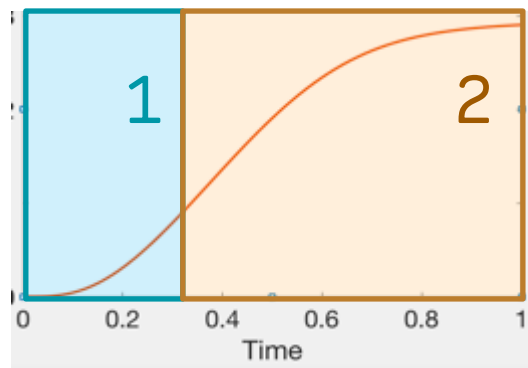
phosphorelay network

- Important signal transduction pathway [Csikász-Nagy et al., J. Royal Soc. Interface, 2011]
- **Aim:** find rate parameters s.t. output has switch-like profile

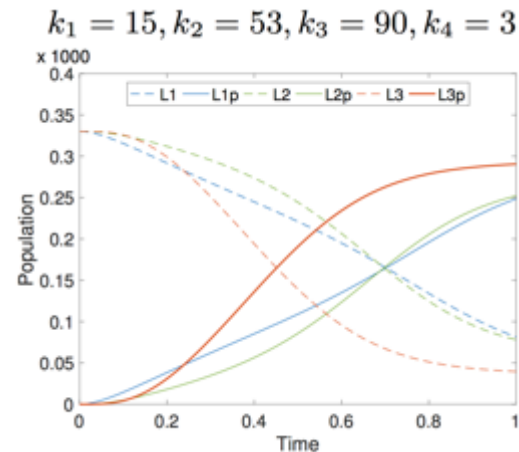
Sketch:



Specification (sigmoid in L3p):



Results



SOLVED IN 370 seconds
(9 ODEs, 7 for species, 2 for
L3p derivatives)

CONCLUSIONS

- Method for synthesis of stochastic CRNs (both rates and structure)
- LNA semantics makes it as scalable as deterministic approximations
 - First language for sketching CRNs
- Optimal synthesis algorithm based on SMT-ODE encoding

FUTURE WORK

- Synthesis from time-series data
- Combination of SMT solving and stochastic search
 - Software tool