Syntax-guided optimal synthesis for chemical reaction networks

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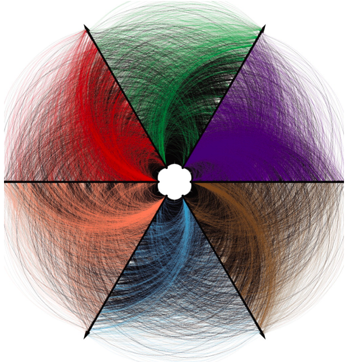
motivation: uncertainty in biological models

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

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

EXAMPLES: network reconstruction, parameter estimation

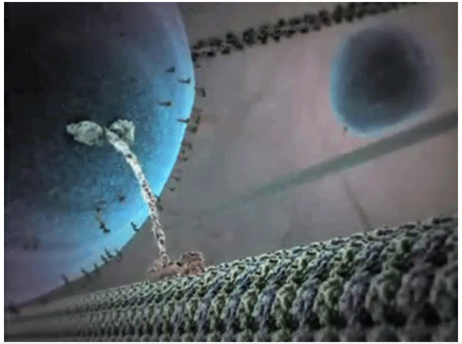
Human Transcription Factor Regulatory Network [Neph et al, Cell 150(6), 2012]



"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



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motivation: uncertainty in biological models

"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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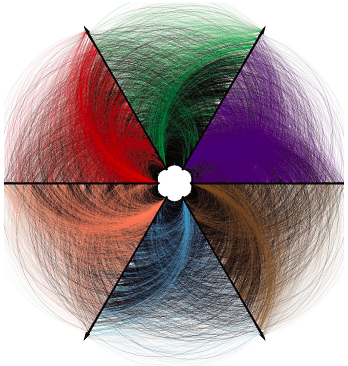

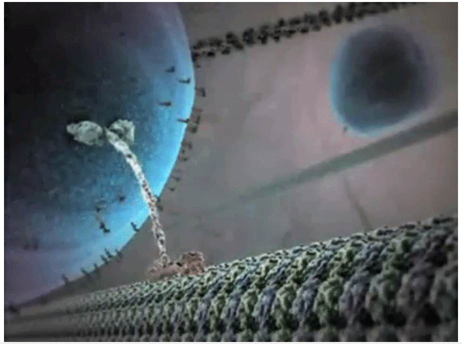

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chemical reaction networks (CRNs)

$$A + 2B \xrightarrow{k} C + D$$

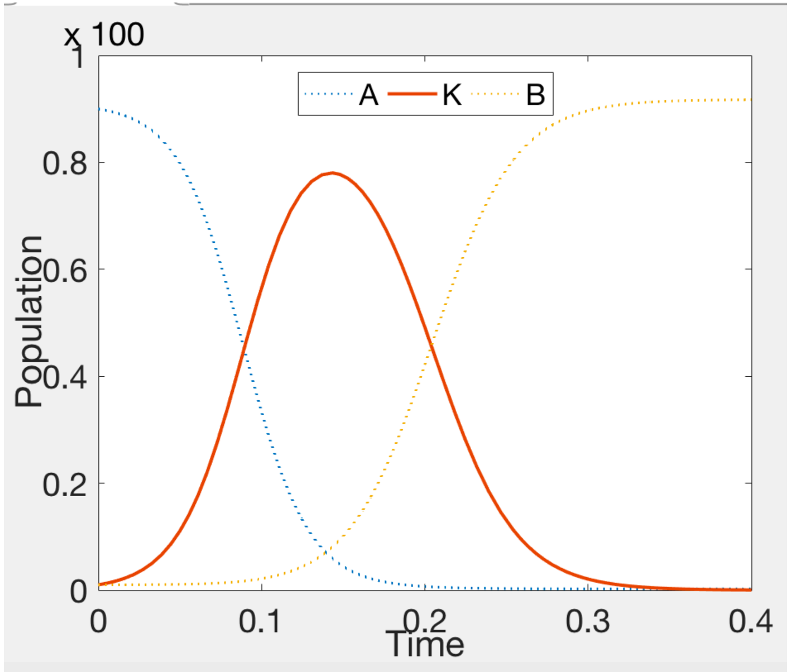
- CRNs are a **fundamental model for natural systems** (chemical, genetic, metabolic, ecological ...)
- **Fundamental computational structure** (equivalent to Petri Nets, Vector Addition Systems, ...)
- Can be "**compiled" into DNA**
- Biochemical interactions are **inherently stochastic** (CRN semantics 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

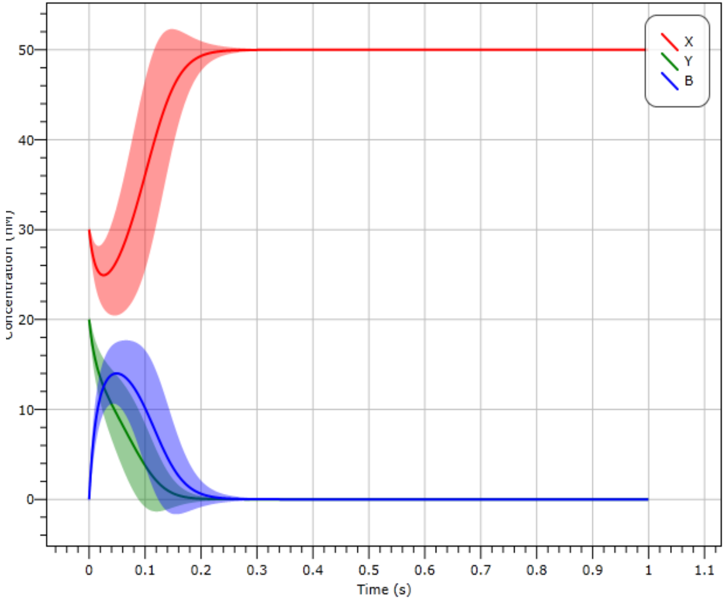
Related work

[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 of 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)

idea 2: syntax-guided program synthesis (SyGuS)

- SyGuS: correctness specification + syntactic template for the program [Alur et al. "Syntax-guided synthesis"]
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CRN sketch example

1) $A + 2B \xrightarrow{10} C + D$

2) $A + 2B \xrightarrow{(0,15]} C + ?$

3) $\{A, C\} + c_1 B \xrightarrow{(0,15]} c_2 B + C + ?$, with $c_1 > c_2$

our approach

- Linear noise approximation (LNA) semantics of CRNs
- 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)

Λ_m={K} and Λ_o= {A, B}

- **Declared variables** for species (λ_i), stochiometric coefficients (c_i), and rates (k_i)
- Variables express the uncertainty

λ_1, λ_2: {A,B},
$c_1,\ldots,c_4$: [0,2],

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

- **Constraints** on initial state and variables

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

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

sketching language – Bell shape example

Species

Λ_m={K} and Λ_o= {A, B}

Declared variables

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Constraints

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

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Reaction sketch

$\tau_1 = \lambda_1 + c_1 K \rightarrow^{k1} c_2 K$

$\tau_2 = \{0,1\}\lambda_2 + c_3 K \rightarrow^{k2} ?\lambda_2 + c_4 K$

$\tau_3 = \varnothing \rightarrow^{k3} \{\lambda_2, [1,2]K\}$

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

Choice between λ_2 and $[1,2]K$

Example instantiation

$A + K \rightarrow^{0.01} 2K$

$B + K \rightarrow^{0.1} 2B$

$\varnothing \rightarrow^{0.001} K$

specification language

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

Bell shape (2 phases):

1

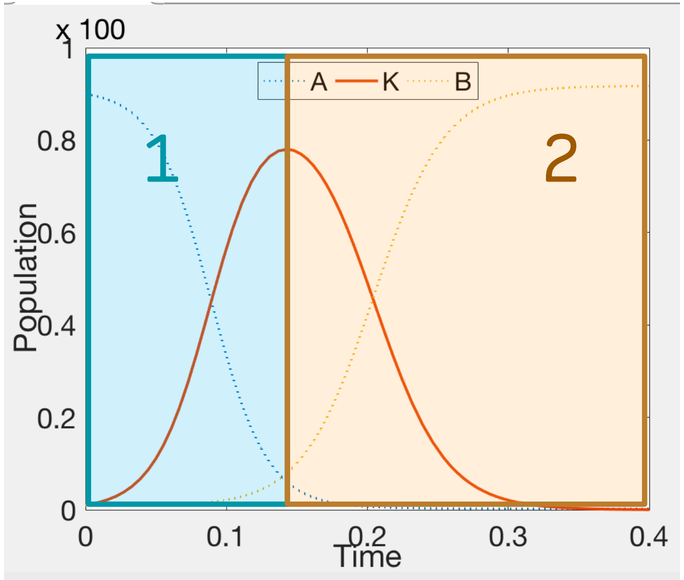
$$\text{inv}_1 \equiv E^{(1)}[K] \geq 0$$

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

2

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

$$\text{pre-post}_1 \equiv E[K]' \leq 1 \wedge T' = 1$$



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:

COST = k_1*(num. of optional species in I) +
k_2*(total num. of reactants in I) +
k_3*(total num. of products in I)

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

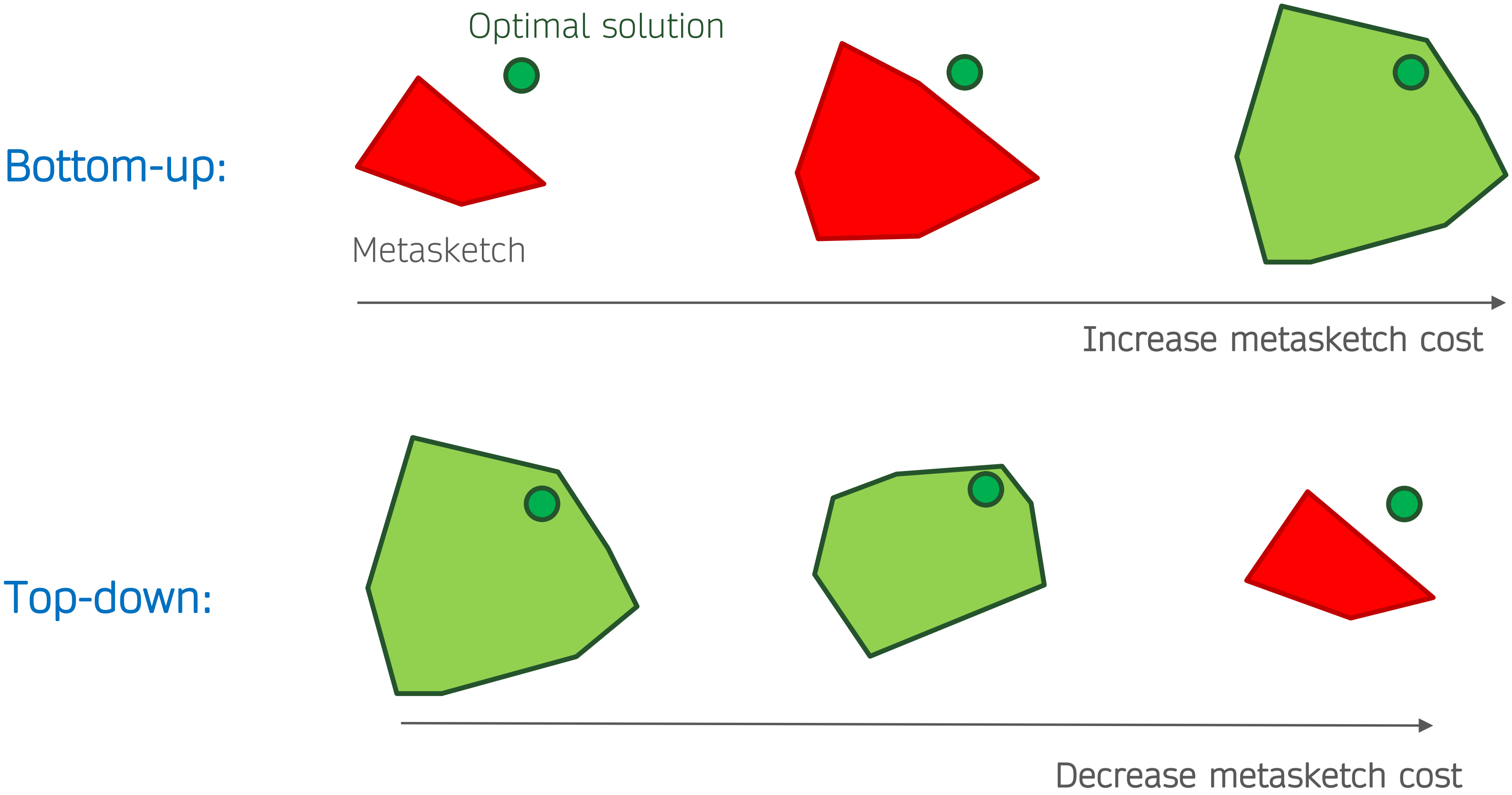
synthesis algorithm

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

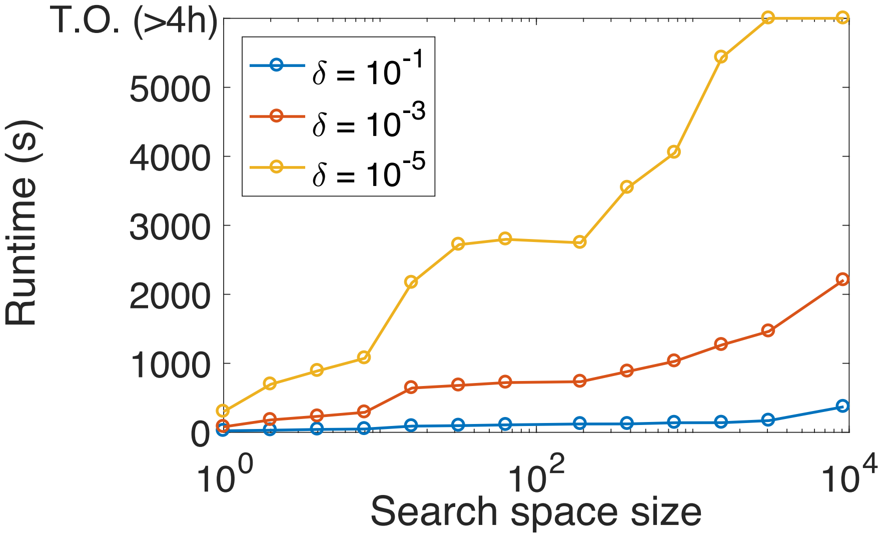
ALGORITHM

- 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



bell shape



- Bottom-up more effective (UNSAT instances are faster)
- 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:

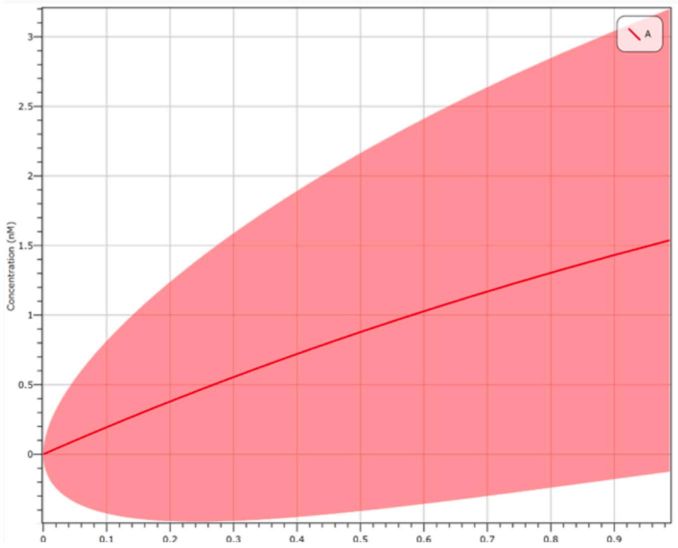
$$\boldsymbol{\tau_1} = \emptyset \rightarrow^{k1} c_1 A + c_2 \lambda_1$$
$$\boldsymbol{\tau_2} = A \rightarrow^{k2} c_3 \lambda_2$$

Specification:

$$inv_1 \equiv C[A] > E[A]$$
$$pre - post_1 \equiv T' = 1$$

Solution:

$$\emptyset \rightarrow^{23} 2A$$
$$A \rightarrow^{94} \emptyset$$



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

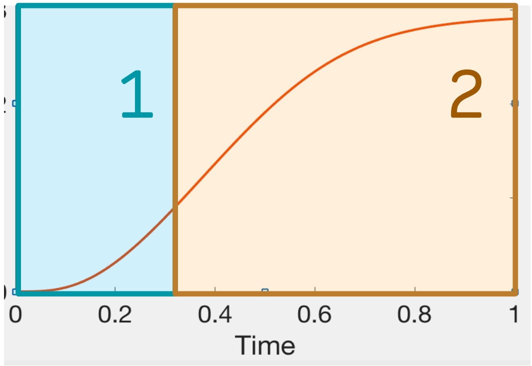
phosphorelay network

- 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:

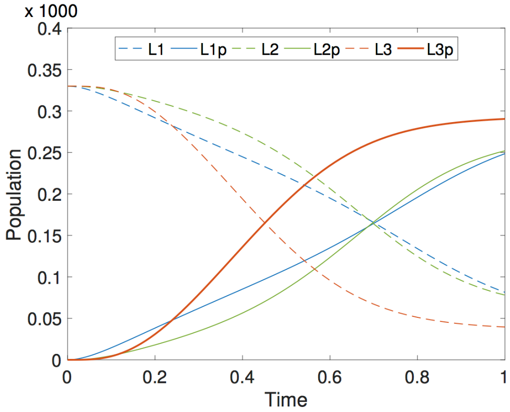
$$L1 + B \xrightarrow{k_1} B + L1p$$
$$L2 + L1p \xrightarrow{k_2} L1 + L2p$$
$$L2p + L3 \xrightarrow{k_3} L2 + L3p$$
$$L3p \xrightarrow{k_4} L3; \quad \emptyset \xrightarrow{1} B$$
$$k_1, \ldots, k_4 : (0, 100],$$
$$Li_0 = 330, Lip_0 = B_0 = 0$$

Specification (sigmoid in L3p):



Results

$$k_1 = 15, k_2 = 53, k_3 = 90, k_4 = 3$$



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

- Explore multiple optimal solutions
- Combination of SMT solving and stochastic search
- Software tool