BioPSy: An SMT-based Tool for Guaranteed Parameter Set Synthesis of Biological Models

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17 September 2015
CMSB

Outline

Introduction

- A key component to modelling biological systems is selecting the correct model parameters (e.g., reaction rate constants).
- Small parameter variations can lead to vastly different results when simulating biological models.
- Methods for performing parameter synthesis and estimation are necessary to determine acceptable values for the parameters of such models.

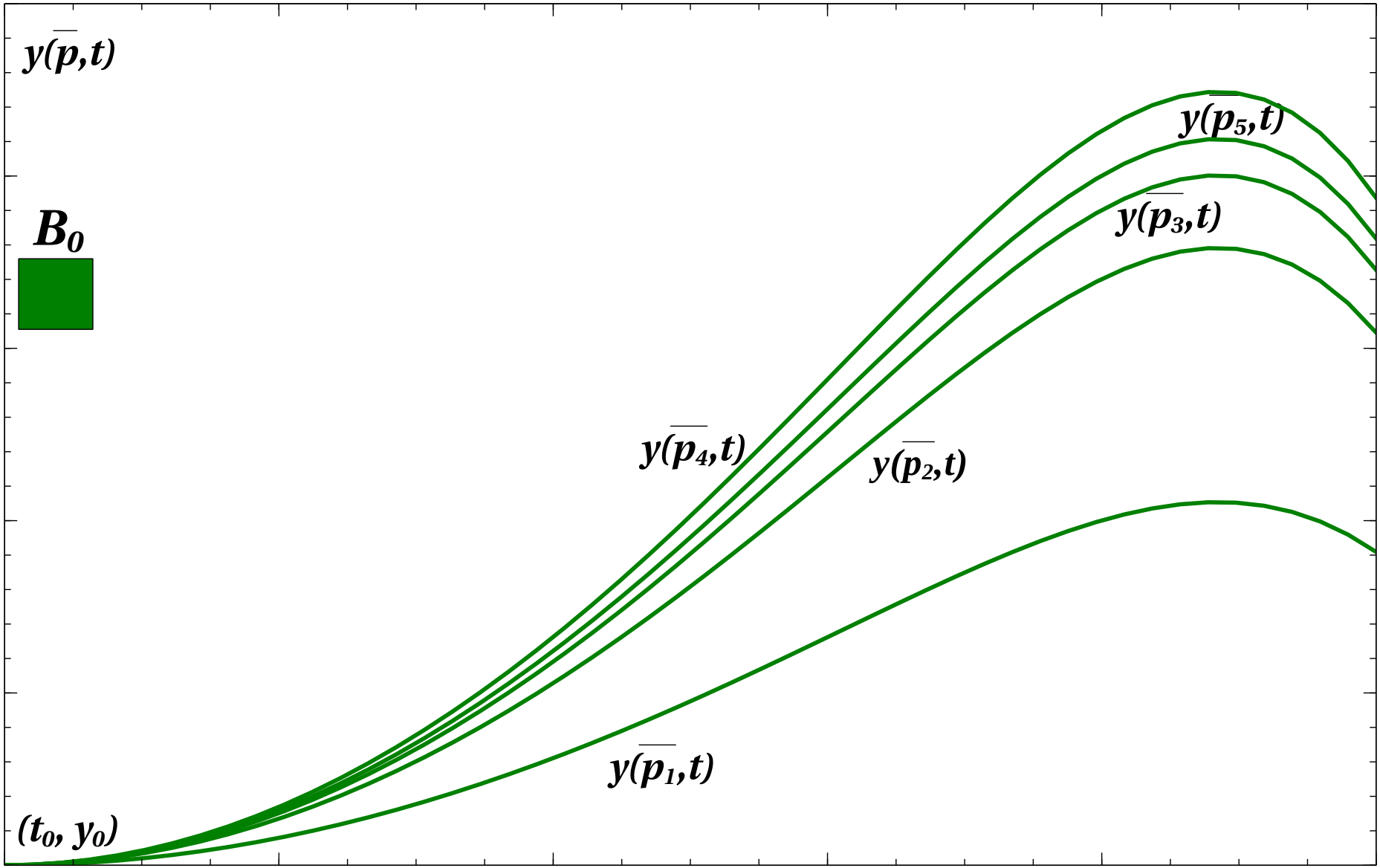
Parameter Synthesis

- The *parameter set synthesis* problem consists of identifying sets of parameter values for which a given system model satisfies a desired behaviour.
- This problem is categorised as a reachability problem where the solution to a set of ODEs can be computed but some parameter values that lead to the solution are missing.
- For example:
  - The parameter, k, can be synthesised in the ODE model given by $x'(t) = kt$.
  - Given the time-series data in which $x = \{0, 1, 4, 9\}$ for $t = \{0, 1, 2, 3\}$, it is easy to see that k should be 2.
  - However, the values of x might vary by 0.1 due to noise.
  - The solution to the parameter synthesis problem might yield the interval $[1.978, 2.022]$ for k.

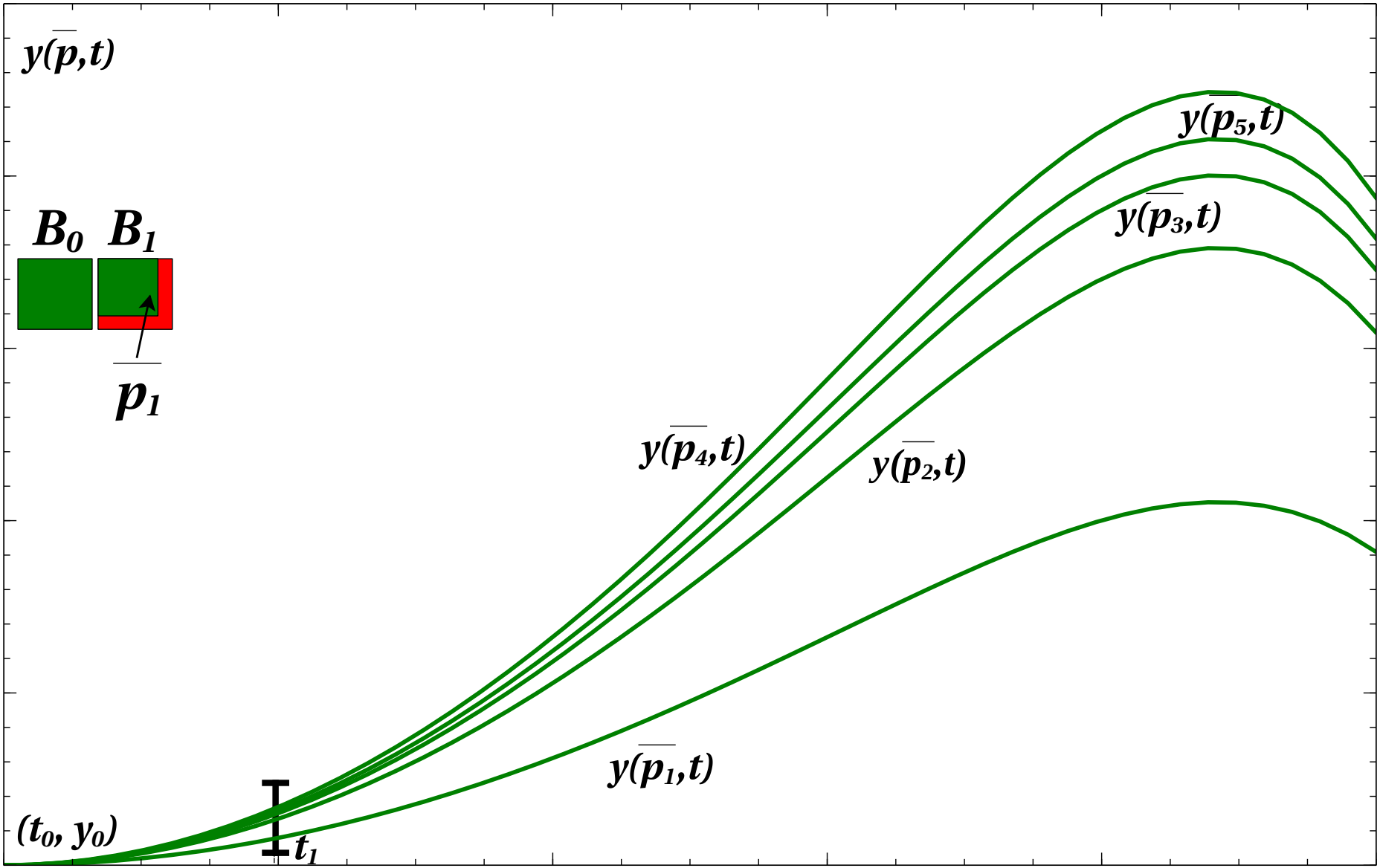
BioPSy

- We have developed BioPSy, a tool for guaranteed parameter set synthesis in biological systems.
- BioPSy is capable of determining *ranges* (intervals) of parameters for which a model's temporal behaviour remains in satisfactory states.
- It takes an SBML model and experimental data as input.
- Additionally, users can specify a list of parameters to synthesise, a tolerable noise value for the experimental data, and the parameter synthesis precision.

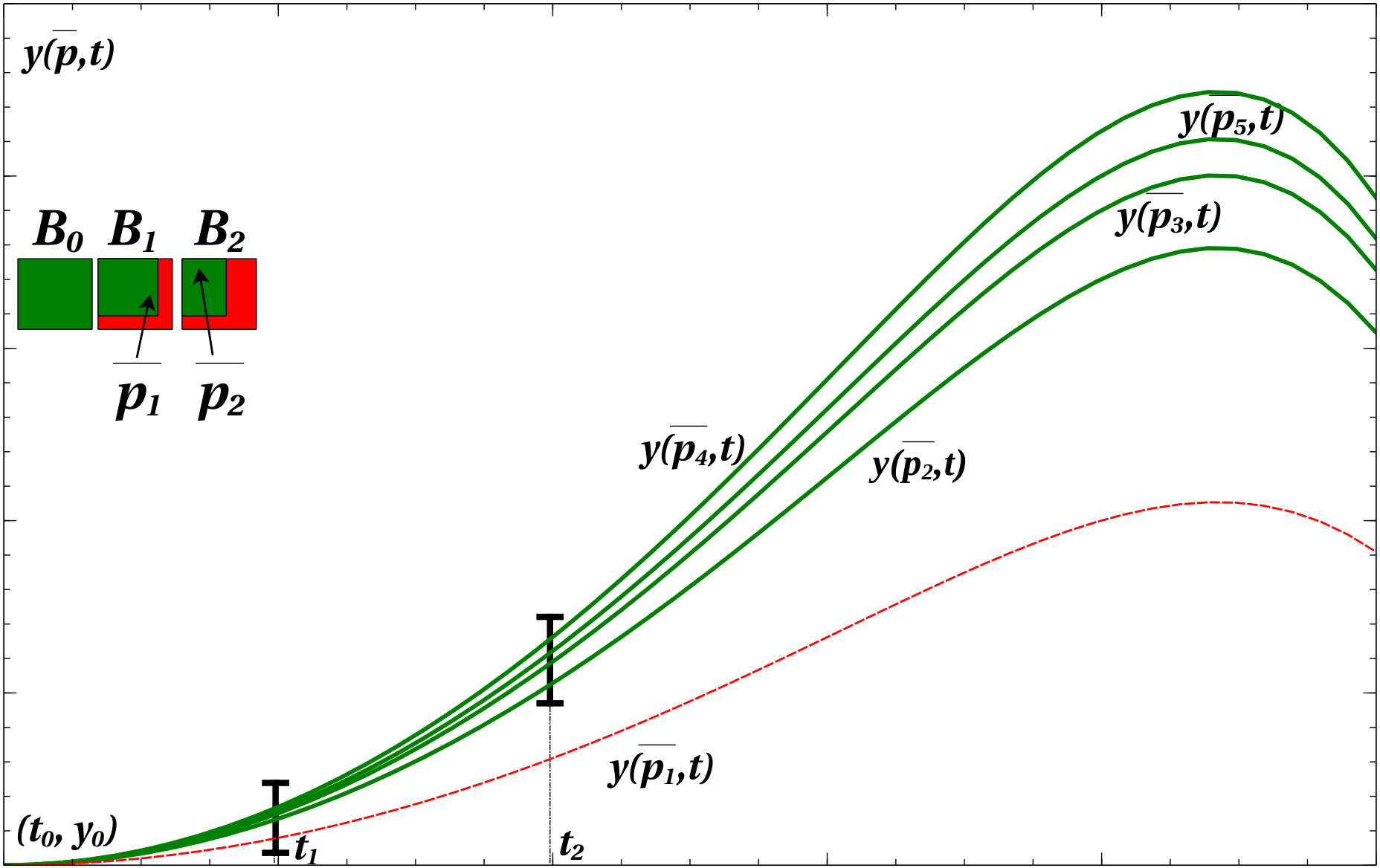
Intuition



Intuition


$y(\bar{p},t)$
B_0 B_1
$\bar{p}_1$
$y(\bar{p}_5,t)$
$y(\bar{p}_3,t)$
$y(\bar{p}_4,t)$
$y(\bar{p}_2,t)$
$y(\bar{p}_1,t)$
(t_0, y_0)
t_1

Intuition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B_0 B_1 B_2
$\bar{p}_1$ $\bar{p}_2$
$y(\bar{p}_5,t)$
$y(\bar{p}_3,t)$
$y(\bar{p}_4,t)$
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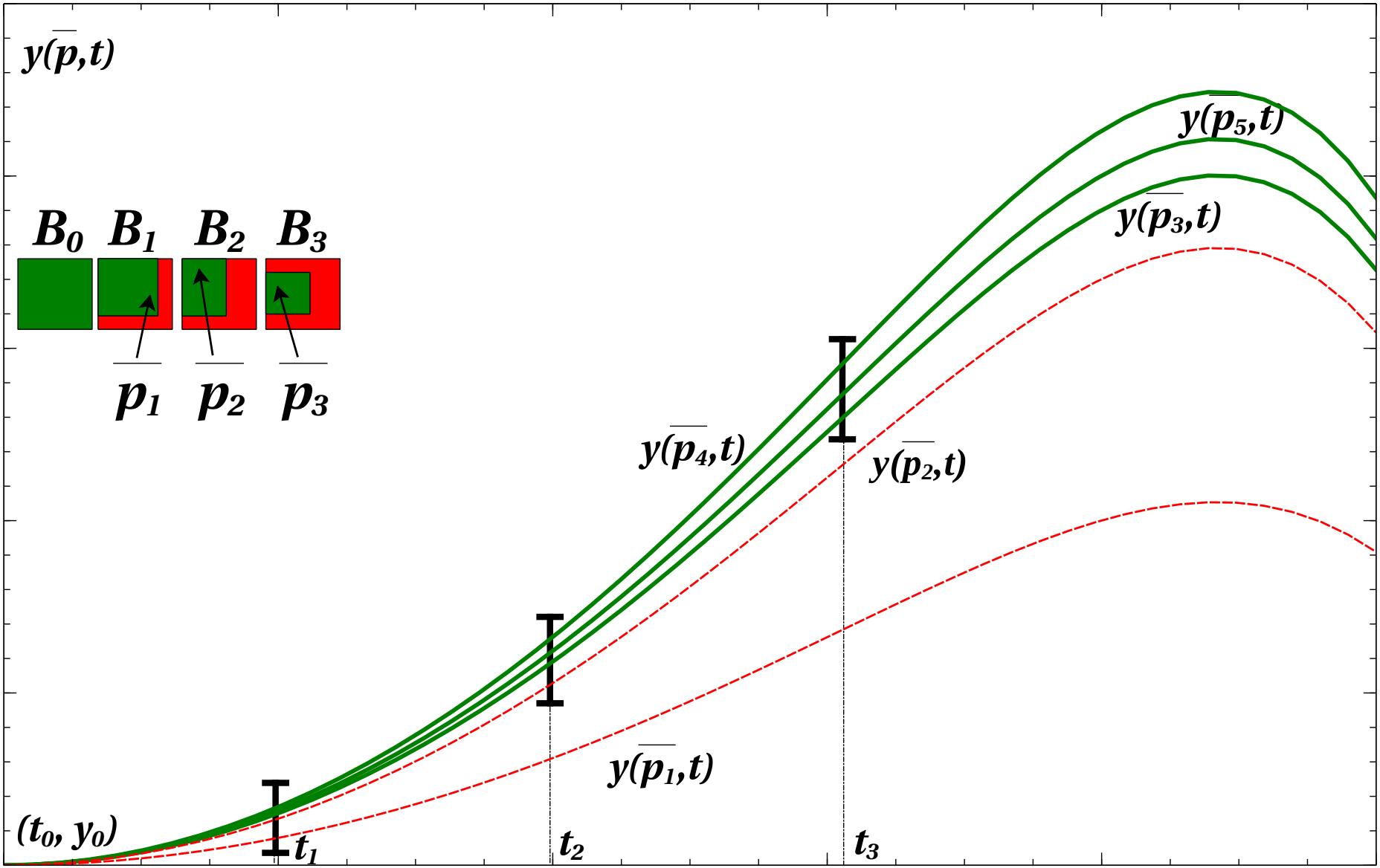
(t_0, y_0)
t_1
t_2

Intuition


$y(\bar{p},t)$
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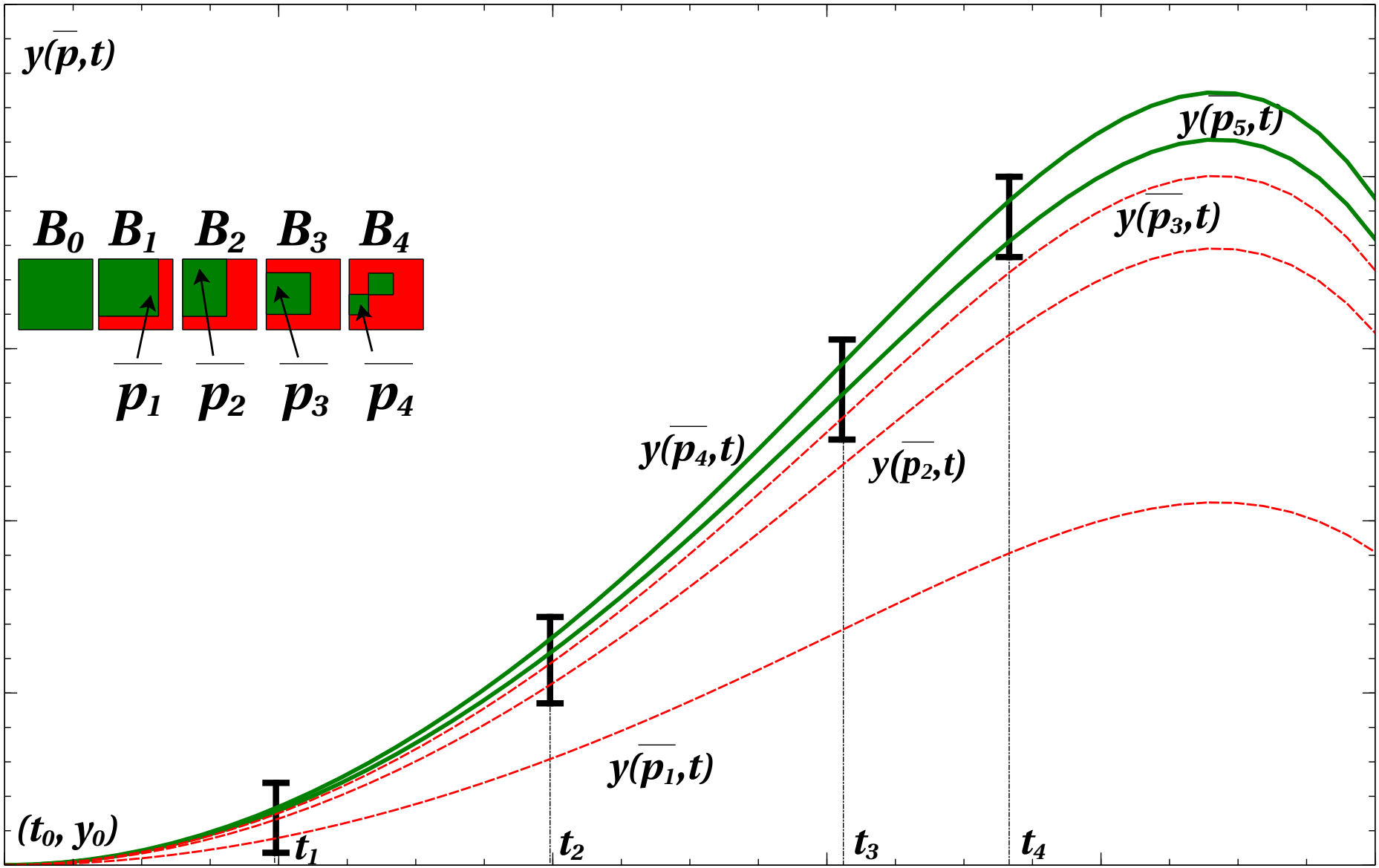
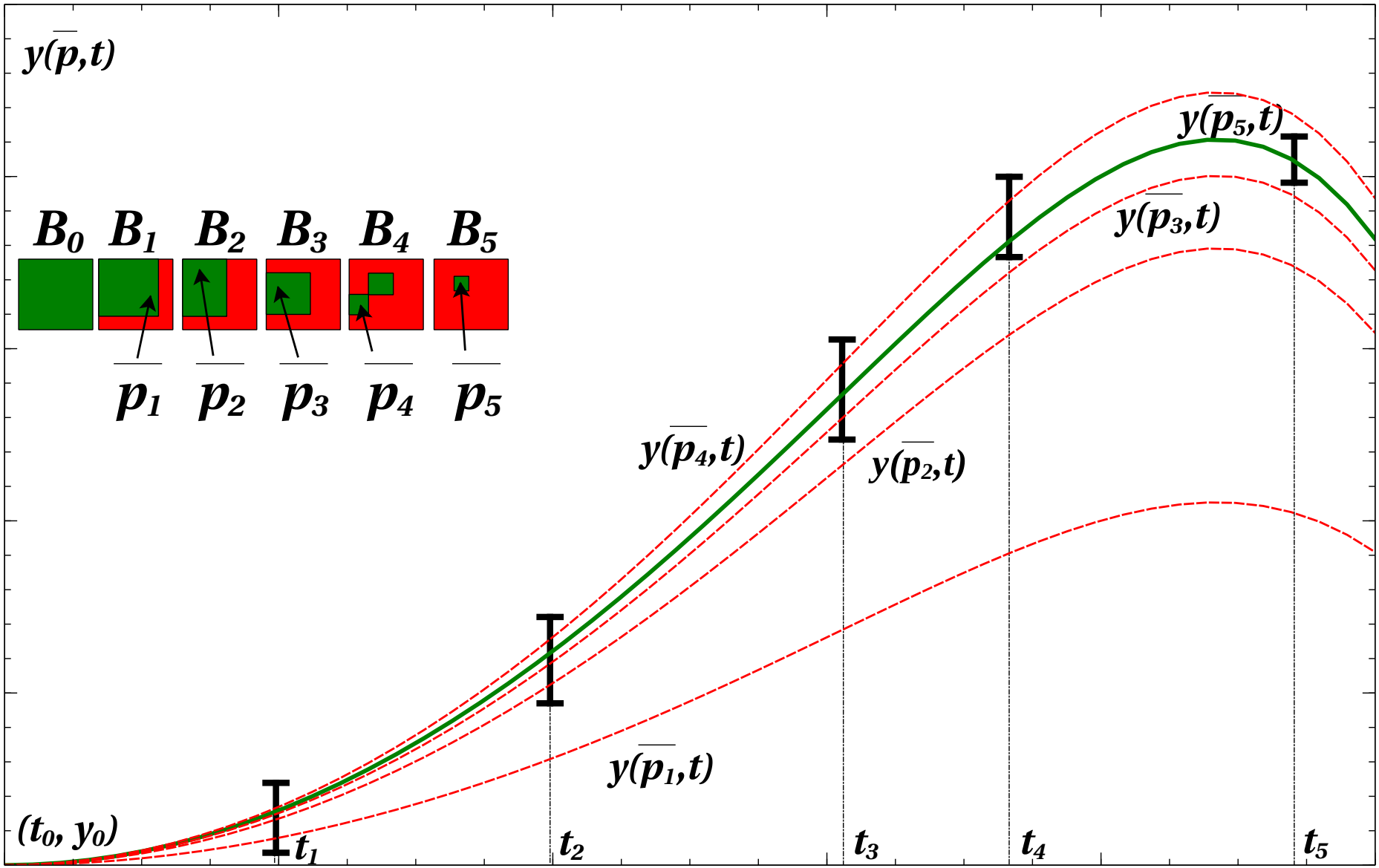
(t_0, y_0)
t_1
t_2
t_3

Intuition


$y(\bar{p},t)$
B_0 B_1 B_2 B_3 B_4
$\bar{p}_1$ $\bar{p}_2$ $\bar{p}_3$ $\bar{p}_4$
$y(\bar{p}_5,t)$
$y(\bar{p}_3,t)$
$y(\bar{p}_4,t)$
$y(\bar{p}_2,t)$
$y(\bar{p}_1,t)$
(t_0, y_0)
t_1 t_2 t_3 t_4

Intuition


$y(\bar{p},t)$
B_0 B_1 B_2 B_3 B_4 B_5
$\bar{p}_1$ $\bar{p}_2$ $\bar{p}_3$ $\bar{p}_4$ $\bar{p}_5$
$y(\bar{p}_5,t)$
$y(\bar{p}_3,t)$
$y(\bar{p}_4,t)$
$y(\bar{p}_2,t)$
$y(\bar{p}_1,t)$
(t_0, y_0)
t_1 t_2 t_3 t_4 t_5

Boxes

- `BioPSy` returns three sets of boxes:
  - A set of **sat** boxes: for all the parameter values in this set, the model is *formally* and *numerically* guaranteed to satisfy the noisy time-series data;
  - A set of **unsat** boxes: for no point in this set, the model satisfies the noisy time-series data; and
  - A set of **undet** boxes: because of the given precision (or due to the undecidability of the problem), `BioPSy` is unable to determine if they satisfy the noisy time-series data.

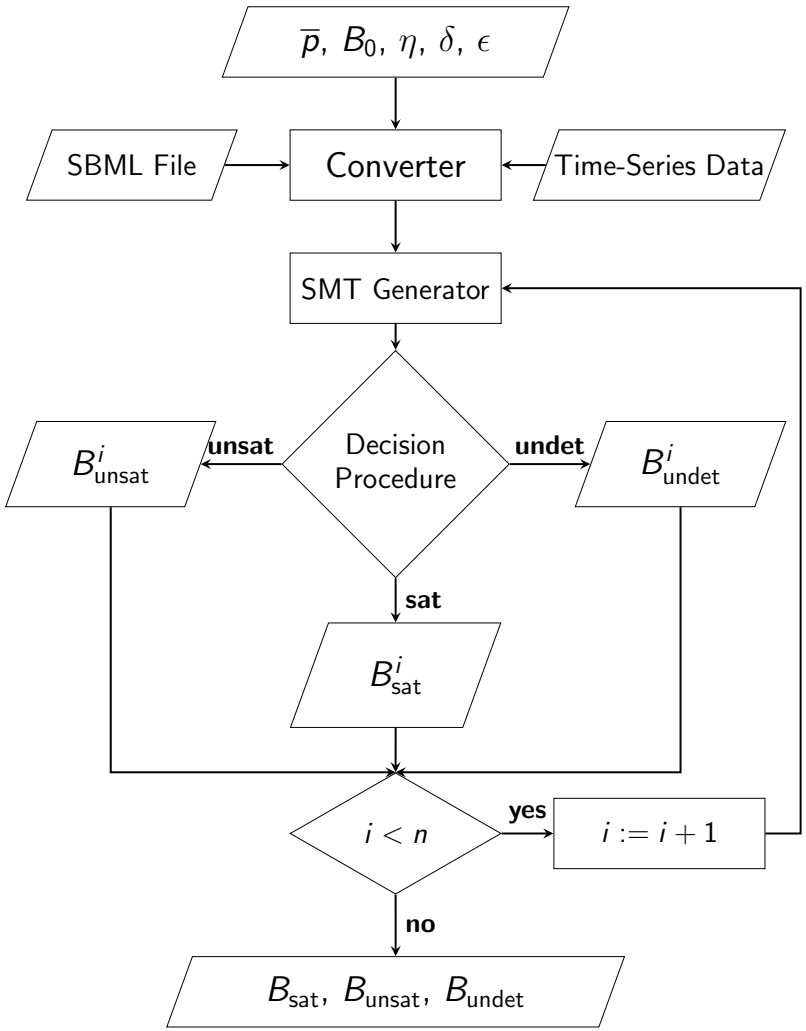
SMT Formulation

- The ODEs (derived from the SBML), parameters, and the noisy time-series data are converted into a collection of SMT problems.
- Each problem represents an *initial value problem* (IVP) constrained by the initial time point and one of the subsequent time points.
- Each individual SMT problem contains assertions that constrain:
  - The solution of each ODE to be contained within the interval found in the noisy time-series data; and
  - The parameters being synthesised to be within the synthesised ranges from the previous time point.

Splitting Boxes

- Initial boxes for the parameter set are passed one-by-one as SMT problems to a decision procedure utilising the SMT solver, `dReal`.
- The synthesis algorithm iteratively splits each box until a minimum size is reached or the current box is either **unsat** or **sat**.
- This process continues incrementally until all the points in the time series are processed.

Algorithm



- δ can be arbitrarily small but must be positive since solving first-order real formulae with general nonlinear functions is an undecidable problem.
- ϵ can be arbitrarily small as well, must also be positive, and determines the level of granularity used to search the parameter space.
- A small η makes it more difficult to identify acceptable ranges but leads to better compliance with the time-series data.

Figure: $\overline{p} = \{p_1, \ldots p_m\}$: model parameters to synthesise, B_0 = initial set of parameter ranges, η = acceptable noise, δ = SMT solver precision, ϵ = precision of parameter synthesis.

Results

- `BioPSy` has been successfully used to synthesise parameter ranges for three models:
  - A personalized prostate cancer therapy model;
  - A cell cycle model; and
  - A human starvation model.

Personalized Prostate Cancer Therapy Model

$$\frac{dx}{dt} = \left(\frac{\alpha_x}{1 + e^{(k_1 - z)k_2}} - \frac{\beta_x}{1 + e^{(z - k_3)k_4}} - m_1 \left(1 - \frac{z}{z_0}\right) - c_1 \right) x + c_2$$

$$\frac{dy}{dt} = m_1 \left(1 - \frac{z}{z_0}\right) x + \left(\alpha_y \left(1 - d_0 \frac{z}{z_0}\right) - \beta_y \right) y$$

$$\frac{dz}{dt} = -z\gamma - c_3$$

$$v = x + y$$

- v - *prostate specific antigen* (PSA)
- x - *hormone sensitive cells* (HSCs)
- y - *castration resistant cells* (CRCs)
- z - androgen

Ideta, A.M., Tanaka, G., Takeuchi, T., Aihara, K.: A mathematical model of intermittent androgen suppression for prostate cancer. Journal of Nonlinear Science 18(6), 593–614 (2008)

Personalized Prostate Cancer Therapy

- A prostate cancer patient was on treatment for 5 nonconsecutive times throughout 6 years and monitored every month (such as PSA and androgen levels were documented).
- Every period of time-series data contains around 4-5 time points.
- Parameter synthesis was performed using real clinical data[1].
- For each time-series, we synthesise $\alpha_y \times \beta_x \in [0.0, 0.05] \times [0.0, 0.05]$ with:
  - Tolerable amount of noise, $\eta = 1.4$;
  - Parameter synthesis precision, $\epsilon = 10^{-3}$; and
  - SMT solver precision, $\delta = 10^{-3}$.

[1] `http://www.nicholasbruchovsky.com/clinicalResearch.html`

Parameter Synthesis

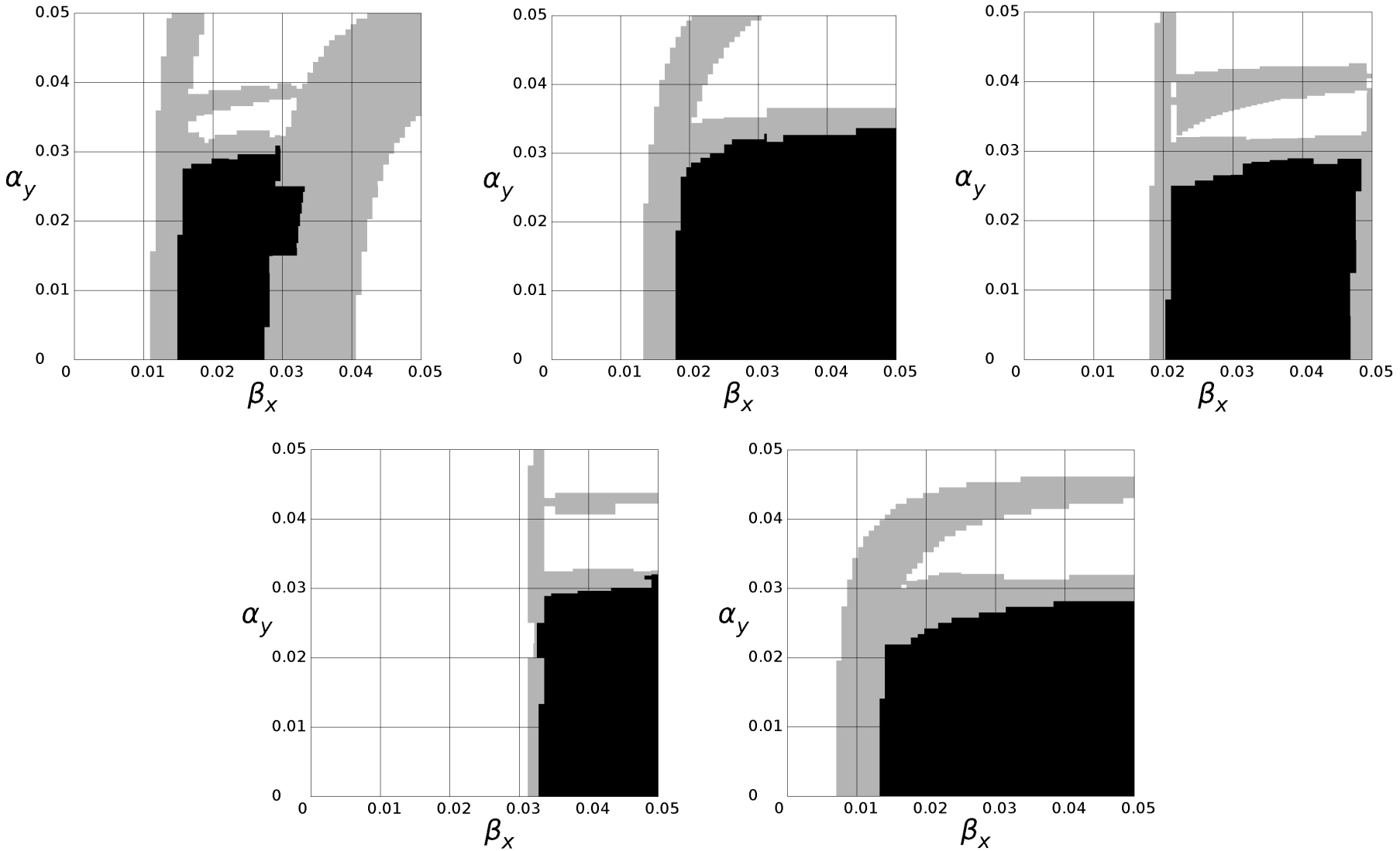


Figure: **white** - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes. **Runtime**: 12 hours for set of time-series data.

Parameter Synthesis Combined Result

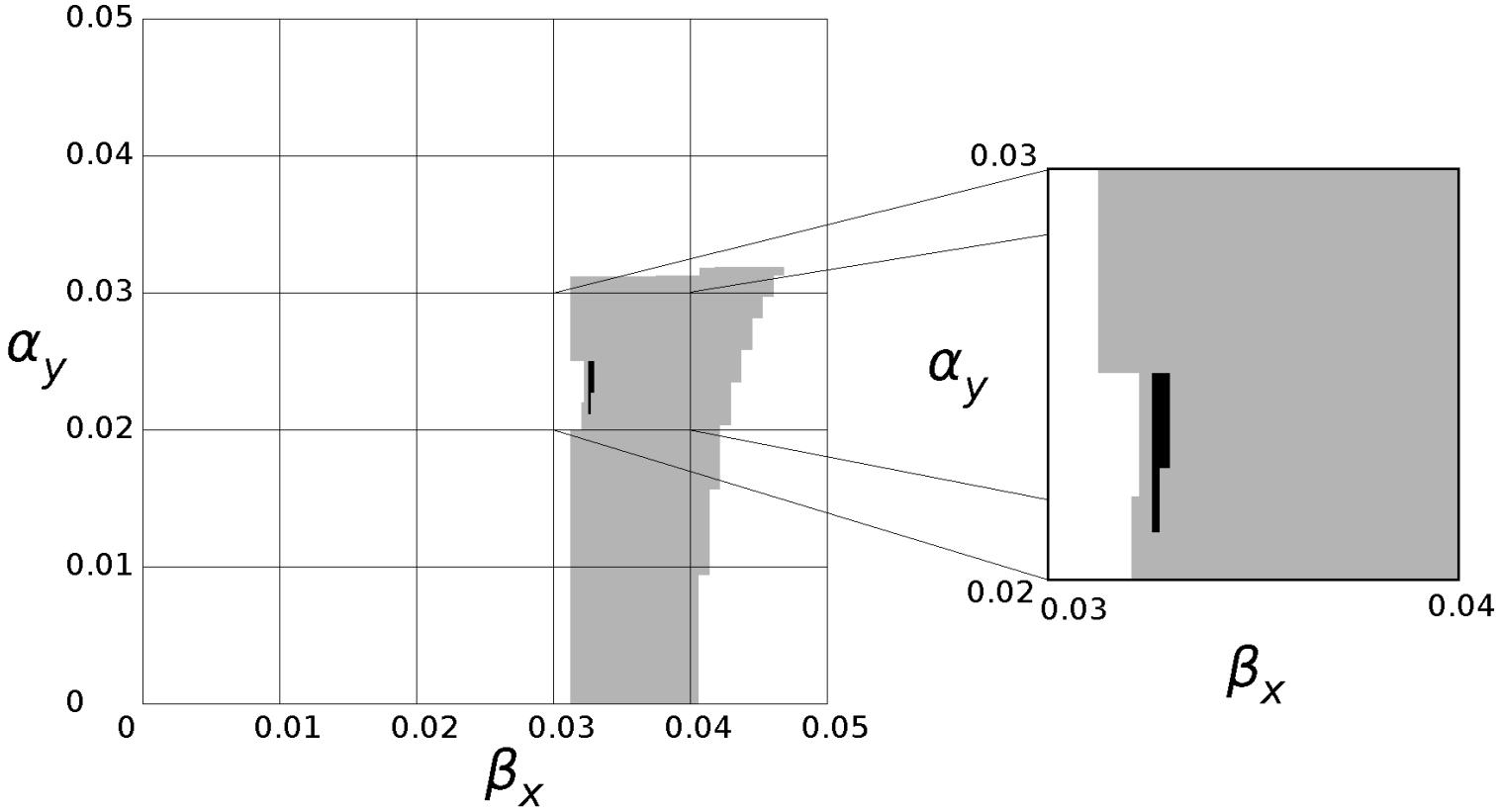


Figure: **white** - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes.

- The feasible set: $\alpha_y \times \beta_x \in [0.0225, 0.025] \times [0.0325, 0.0332031] \bigcup [0.0210938, 0.0225] \times [0.0325, 0.0327344]$.

Parameter Checking

- Checking parameter values is easier than synthesising parameter sets.
- Parameter values in this study were obtained using `COPASI` and verified with `BioPSy`.

Method	α_x	α_y	β_x	β_y	`BioPSy`				
					S_1	S_2	S_3	S_4	S_5
Evolut. Prog.	-0.216	-2.68×10^{-6}	0.0272	0.000135	n	y	y	n	y
Hooke & Jeeves	-0.309	-0.279	0.029	-0.24	y	y	y	y	y
Levenberg-Marquardt	-0.17	-32.0	0.00661	-10.5	n	n	n	n	n
Praxis	-0.233	-0.00698	0.0240	0.187	y	y	y	n	y
Scatter Search	-0.17	-31.9	0.00661	-10.5	n	n	n	n	n
Simulated Annealing	-0.249	6.4×10^{149}	0.0227	-2.27×10^{148}	n	n	n	n	n
Truncated Newton	-0.236	-0.00792	0.0244	0.0116	y	y	y	n	y

Cell Cycle

- In this model, two proteins, CDC2 and Cyclin, combine to form a heterodimer.
- The heterodimer controls major events in a cell causing it to:
  - Reach a steady state;
  - Act as a spontaneous oscillator; or
  - Act as an excitable switch.
- The cell cycle model has reference BIOMD0000000006 in the BioModels Database[2].
- The simulated time-series data contains 10 time points.

Tyson, J.J.: Modeling the cell division cycle: cdc2 and cyclin interactions. Proceedings of the National Academy of Sciences 88(16), 7328–7332 (1991)

[2] `https://www.ebi.ac.uk/biomodels-main/`

Cell Cycle Model

- For this experiement, we synthesise $k_4' \times k_4 \in [0.01, 0.02] \times [175, 185]$ with:
  - Tolerable amount of noise, $\eta = 10^{-3}$;
  - Parameter synthesis precision, $\epsilon = 0.1$; and
  - SMT solver precision, $\delta = 10^{-3}$.

$$\frac{du}{dt} = k_4 (v - u) \left(\frac{k_4'}{k_4} + u^2 \right) - k_6 u$$
$$\frac{dv}{dt} = \kappa - k_6 u$$

- u - CDC2
- v - Cyclin

Parameter Synthesis

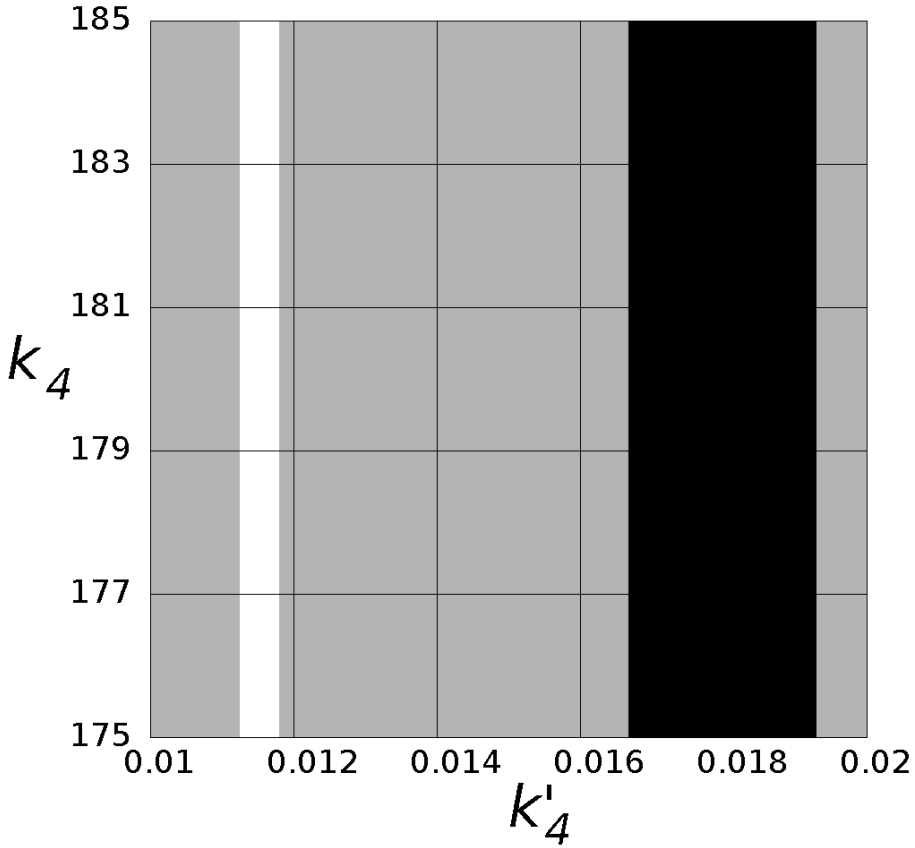


Figure: **white** - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes. **Runtime**: 10 minutes.

- The feasible set: $k'_4 \times k_4 \in [0.0166691, 0.0192934] \times [175, 185]$.

Human Starvation

- The human starvation model tracks the amount of fat, protein in muscle mass, and ketone bodies in the human body after glucose reserves have been depleted.
- For this experiement, we synthesise $\kappa \times b \in [9, 11] \times [0.05, 0.08]$ with:
  - Tolerable amount of noise, $\eta = 0.1$;
  - Parameter synthesis precision, $\epsilon = 0.1$; and
  - SMT solver precision, $\delta = 10^{-3}$.
- The simulated time-series data contains 25 time points.

$$(\text{Fat})\frac{dF}{dt} = F\left(\frac{-a}{1+K} - \frac{1}{\lambda_F}\left(\frac{C + gL_0}{F+M} + \kappa\right)\right)$$

$$(\text{Protein})\frac{dM}{dt} = -\frac{M}{\lambda_M}\left(\frac{C + \kappa L_0}{F+M} + \kappa\right)$$

$$(\text{Ketone Bodies})\frac{dK}{dt} = \frac{VaF}{1+K} - b$$

Song, B., Thomas, D.: Dynamics of starvation in humans. Journal of Mathematical Biology 54(1), 27–43 (2007)

Parameter Synthesis

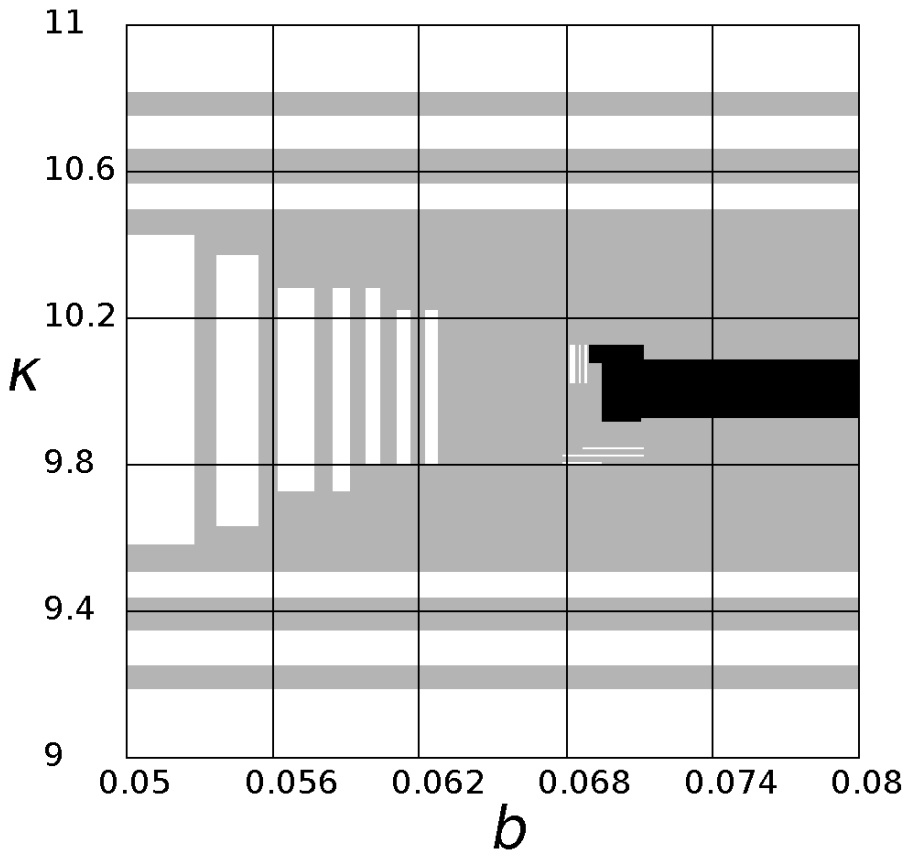


Figure: **white** - infeasible boxes; **black** - feasible boxes; and **gray** - undetermined boxes. **Runtime**: 5 minutes.

- The feasible set: $\kappa \times b \in [9.88077, 9.8832] \times [0.0764844, 0.0771875] \bigcup [9.92213, 10] \times [0.0785938, 0.08] \bigcup \ldots$.

BioPSy Demo Video

Conclusions

- `BioPSy` accepts SBML models, so it can be applied to a large number of existing biological models.
- The tool is not only limited to biological models with mass action kinetics but can handle models involving general ODEs.
- Models using parameters synthesised with `BioPSy` are formally guaranteed to behave as desired.
- Also, parameter estimates generated by other methods can be formally validated with `BioPSy`.
- `BioPSy` is freely available for download from: `https://github.com/dreal/biology`.

Future Work

- We hope to improve `BioPSy` to suggest how to proceed with undecidable ranges:
  - The tool could automatically synthesise the parameters again with a finer level of precision; and/or
  - Undecidable ranges that lie right next to each other could be automatically combined into a larger interval and re-analysed.
- Additionally, we plan to extend `BioPSy` to handle biological models that contain both continuous and discrete dynamics.

Thank you

Questions?