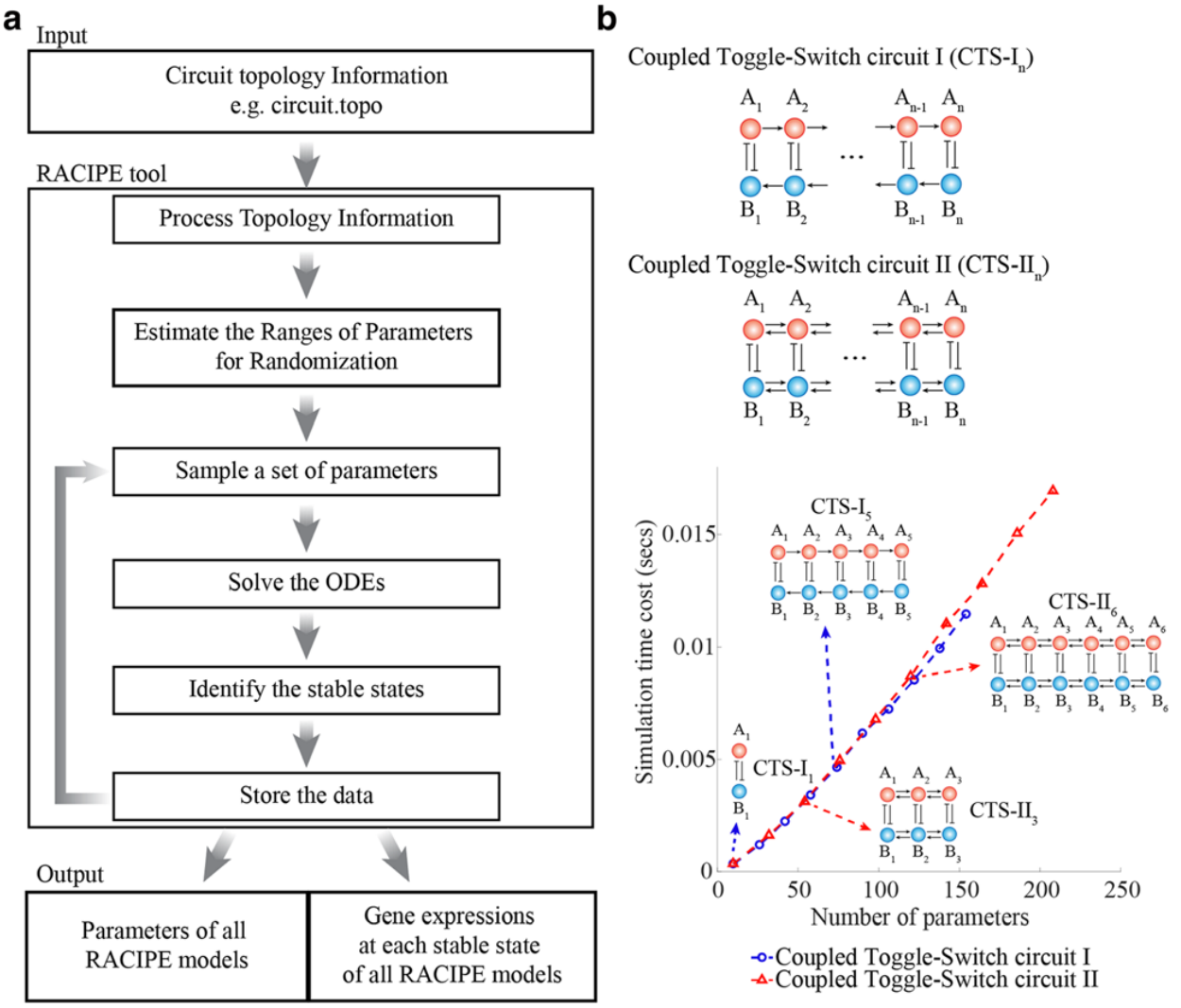

Fig. 1 The computational tool of random circuit perturbation (**a**) Workflow of RACIPE. The only input for the tool is the circuit topology information. RACIPE automatically estimates the ranges of kinetic parameters for randomization and, from these ranges, randomly samples a particular set of parameters for a model. Then, it simulates the rate equations for this model to find all possible stable states. This procedure is repeated for many times to generate an ensemble of models. Finally, the tool outputs, from all the models, the kinetic parameters and the simulated gene expression of all stable states. **b** RACIPE is tested on two types of coupled toggle-switch (CTS) circuits (diagram illustrated in the top panel). The arrows represent transcriptional activation; the bar-headed arrows represent transcriptional inhibition. For both of the cases, the average time cost to simulate a RACIPE model (y-axis) is linearly proportional to the number of model parameters (x-axis)

Time cost of simulations

To evaluate the performance of the tool with different choices of simulation parameters, we test the tool on two types of coupled toggle-switch (CTS) circuits (Fig. 1b, see Additional file 1: SI section "Results" for mathematical models). They both contain several toggle-switch motifs, but different connecting patterns among these motifs, where the type I circuits (CTS-I) have unidirectional activations among A genes (B genes), while the type II circuit (CTS-II) have mutual activations among A genes (B genes). These circuits have been actively studied to understand the coupled cellular decision-making processes [37, 38]. By changing the number of toggle-switch mo- tifs, we can easily test RACIPE on circuits of different sizes. For each circuit, we generate 10,000 random models and solve steady-state expressions starting from 1000 initial conditions for

each model. As shown in Fig. 1b, for both types of circuits, the average simulation time to solve a RACIPE model scales linearly with the total number of parameters in the model, suggesting its potential use on large circuits. Of note, the total time to simulate all RACIPE models depends on other factors (the number of models, the number of initial conditions, etc.), which will be discussed in the next section.

Source

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