Automated Probing and Inference of Analytical Models for Metabolic Network Dynamics

JOHN WIKSWO, Vanderbilt University, MICHAEL SCHMIDT, Cornell University, JERRY JENKINS, Hudson Alpha Institute, JONATHAN HOOD, CFD Research Corp, HOD LIPSON, Cornell University — We introduce a method to automatically construct mathematical models of a biological system, and apply this technique to infer a seven-dimensional nonlinear model of glycolytic oscillations in yeast — based only on noisy observational data obtained from in silico experiments. Graph-based symbolic encoding, fitness prediction, and estimation-exploration can for the first time provide the level of symbolic regression required for biological applications. With no a priori knowledge of the system, the Cornell algorithm in several hours of computation correctly identified all seven ordinary nonlinear differential equations, the most complicated of which was

$$\frac{d A_3}{d t} = -1.12 \cdot A_3 - \frac{192.24 \cdot A_3 \cdot S_1}{1 + 12.50 \cdot A_3} + 124.92 \cdot S_3 + 31.69 \cdot A_3 \cdot S_3,$$

where $A_3 = [ATP]$, $S_1 = [glucose]$, and $S_3 = [cytosolic pyruvate and acetaldehyde pool]$. Errors on the 26 parameters ranged from 0 to 14.5%. The algorithm also automatically identified new and potentially useful chemical constants of the motion, e.g. $-k_1 \cdot N_2 + K_2 \cdot v_1 + k_2 \cdot S_1 \cdot A_3 - (k_4 - k_5 \cdot v_1) \cdot A_3^2 + k_6 \approx 0$. This approach may enable automated design, control and analysis of wet-lab experiments for model identification/refinement.

1Supported in part by DTRA, NIAID, NIDA, NSF and VIIBRE

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